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Original Scientific Paper

SUGGESTIVE PREPARATION OF PATIENTS USING INTRAVENOUS KETOPROFEN AS A PART OF POSTOPERATIVE PAIN MANAGEMENT IN ELECTIVE ABDOMINAL SURGERY

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SUMMARY – Suggestive preparation before surgery may have a placebo effect and can reduce perioperative consumption of analgesics. A total of 77 adult patients undergoing elective cholecystectomy and hernioplasty were included in this prospective study. All patients were given 100 mg of ketoprofen intravenously and were assigned to two groups. The first group was not informed about analgesia (no preparation, NP group), and the second group were told that they will receive a strong painkiller (suggestive preparation, SP group). Pulse rate, blood pressure and VAS scores were registered in all patients immediately before anesthesia induction in the operating room (T1), after waking up in the recovery room (T2), 6 hours after surgery at the surgical ward (T3) and on the morning after surgery in the surgical ward (T4), at rest and during movement. Rescue nonsteroidals were offered to patients with VAS 3-4, and opioids for VAS ≥5. The patients in the SP group had lower VAS scores in all measurements and lower opioid consumption. A statistically significant difference was observed in VAS2 measurement during movement (3 [2-5] vs. 2 [0-3.75] in the NP and SP group, P=0.008). SP had a placebo effect and reduced VAS scores as well as opioid consumption.

Key words: *placebo effect; suggestion; ketoprofen; acute postoperative pain; visual analog scale.*

Introduction

Suggestive preparation can influence the experience of pain after the use of a placebo. It was shown that the suggestion activates a cascade of neurochemical-electrophysiological alterations in different brain areas[1]. Suggestive preparation has been examined in earlier studies with the aim of achieving an analgesic effect in humans. Wager et al. confirmed that the experience of pain after thermal stimulation was reduced after convincing healthy volunteers of the analgesic effect of the substance to be applied[2]. The same was observed in a recent study by Benson et al., where expectation reduced the perception of pain in a visceral pain study[3].

Ketoprofen is nonsteroidal, non-selective anti-inflammatory drug, effective in both acute and chronic pain treatment[4] The use of ketoprofen 12.5-100.00 mg may result in effective postoperative pain relief in 50% of patients with moderate to severe acute postoperative pain[4]. A newer derivative of ketoprofen, dexketoprofen, was introduced into clinical praxis with the aim of

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better pain control and reducing side effects, but clinical evidence did not confirm these expectations[4]

Boccara et al. confirmed that ketoprofen was successful as an analgesic in patients after elective cholecystectomy[5]. Its effectiveness was superior when compared with saline and compared with propacetamol. Additionally, a better analgesic effect was achieved when ketoprofen was administered before surgery compared with postoperative administration[5]. In another study performed by Toivonen et al., ketoprofen was effective for postoperative pain relief as part of a multimodal analgesic approach after operative treatment of inguinal hernia[6]. It is not known whether suggestive preparation can reduce the VAS scores in patients who received intravenous ketoprofen for postoperative analgesia.

The aim of this study was to measure the effects of ketoprofen on postoperative pain. Our aim was to examine whether suggestive preparation would affect blood pressure values, pulse, postoperative pain, nausea and vomiting, and opioid consumption in patients who received ketoprofen for postoperative analgesia in moderately invasive surgical procedures, namely laparoscopic cholecystectomy and inguinal hernioplasty. The data were compared with the demographic characteristics of the patients.

Patients and methods

This study was conducted at the Department of Anesthesiology, Resuscitation and Intensive Care and at the Department of Abdominal Surgery in the Osijek University Hospital. The study was approved by the Ethics Committee of the Osijek University Hospital and Ethics Committee of the Faculty of Medicine no 25-1:568-4/2014. The study investigating the use of ketoprofen for postoperative analgesia was carried between January 2014 and January 2016.

On the morning of the surgery, all patients were examined in the premedication room by an anesthesiologist, and their demographic data were recorded, including age, gender, body mass index, comorbidities and drugs taken. The patients' physical status was assessed using the ASA classification. The patients were informed about the prospective study and signed the informed consent form. All patients were told that their postoperative pain would be measured, the VAS scale was explained to them and they were told that pain would be recorded immediately before anesthesia induction in the operating room (VAS1), after waking up in the recovery room (VAS2), 6 hours after surgery at the surgical ward (VAS 3) and on the morning after surgery in the surgical ward (VAS4). All patients were told that, depending on how much pain they feel, they would receive additional pain-relieving medication. After that, by random selection of even and odd numbers, the patients were assigned to the two groups. The first group received analgesia with ketoprofen, without suggestive preparation (NP, odd numbers). Patients weighing up to 90 kg received 100 mg of ketoprofen, and those weighing ≥90 kg received 200 mg in infusion. The nurse then added ketoprofen to the infusion, without describing what she was doing. The second group underwent a suggestive preparation. The patients were told that they would receive a strong painkiller (SP, even numbers). The nurse then added ketoprofen to the infusion at the specified dose in front of the patient. The patients were told that they may rarely but occasionally still feel pain after receiving the medication and that they would be asked at scheduled time intervals about how much pain they felt.

Preoperatively, after the monitor in the operating room was turned on, all patients had their heart rate, blood pressure, VAS at rest and VAS during movement measured.

During the 24 hours after surgery, all medications, non-steroidal analgesics and opioids that the patient received were recorded. All the patients were offered additional ketoprofen up to 300 mg daily for pain <4 on the VAS scale, or tramadol 50-100 mg if their pain was 5 or more. Patients were offered morphine or meperidine for severe and breakthrough pain during the movement or coughing.

Postoperative nausea and vomiting (PONV) were registered in the recovery room (PONV1) and 24 hours after the surgery on the surgical ward (PONV2). It was scored as 0 – no PONV, 1 – transitory nausea, 2 – continuous nausea, 3 – continuous nausea and vomited once, and 4 – vomited more than once.

The study included 85 adult patients undergoing elective surgical procedures, laparoscopic cholecystectomy and inguinal hernioplasty. After the data were analysed, 8 patients were excluded: 1 was given wrong drug, 1 refused further investigation after surgery, no group was recorded in two cases, 1 patient reported severe pain when placed on the operating table, and postoperative data were missing in 3 patients. Finally, 77 patients were included in the study.

The statistical analysis was done using MS Excel and the IBM Statistical Package for Social Sciences (SPSS) 22.0 statistical software (IBM SPSS Statistics; Armonk, NY, USA). Data distribution was performed using the Kolmogorov-Smirnov test. Since data were not normally distributed, continuous variables were shown as median and interquartile. A Mann-Whitney test for continuous and Fisher's exact test for categorical variables was calculated. The relationship between demographic parameters, drug use and pain were calculated using Pearson correlation. P<0.05 was considered statistically significant.

Results

A total amount of 77 adult patients undergoing elective cholecystectomy and hernioplasty were included in the prospective study. Table 1 shows the differences between the sexes, ASA status, drugs used and comorbidities between group A and group B. There was no any statistically significant difference in the incidence of comorbidities between groups (Table 1).

Table 1. The demographic characteristics of study patients

	NP, Ketoprofen, (n=39)	SP, Ketoprofen (n=38)	P
M/F	19 / 20	25 / 12	0.058
Age	53 [45-68]	52 [46-64]	0.633
BMI	27.7 [24.7-32.1]	29.8 [24.9-31.6]	0.933
ASA 1 / 2 / 3	36 / 3	32 / 6	0.268
Drugs used	2 [2-2]	2 [1-2]	0.159
Comorbidities			
Cardiac	6 / 33	3 / 35	0.480
Hypertension	22 / 17	15 / 23	0.136
Renal	3 / 36	0 / 38	0.240
Metabolic	10 / 29	11 / 27	0. 744
Respiratory	2 / 37	3 / 35	0.675
Psychiatric	6 / 33	4 / 34	0.737
Other	9 / 30	3 / 35	0.114

Comparing the demographic data between patients in group NP and group SP, there were no statistically significant differences. The average body mass index of all subjects was 28.5±4.8, and there were no significantly differences between group A and group B.

In the whole study group (N=77), only 25 patients (32.5%) had no associated diseases. In the NP group, 33 patients (84.6%) had associated diseases, as did 19 out of 38 (50.0%) in group B. The most common associated disease was hypertension, which was registered in 56.4% patients in group NP and in 39.4% in group SP. Metabolic diseases were registered in 25.6 and 28.9% patients in group NP and SP, respectively. There was no difference in the incidence of associated diseases among groups.

Perioperative drug consumption and postoperative nausea and vomiting in the two groups are shown in Table 2.

Table 2. Intraoperative and postoperative drug consumption and postoperative nausea and vomiting in perioperative surgical patients

	NP, Ketoprofen, (n=39)	SP, Ketoprofen (n=38)	P
Intraoperative opioids (ME)	30 [23.75-45]	27.5 [20-30]	0.250
Ketoprofen intraoperative	100 [100-100]	100 [100-200]	0.157
NSAIDs doses (postoperative / 24h)	1 [1-2]	1 [0-2]	0.312
Patients needed postoperative opioids (N)	12 / 27	5 / 33	0.062
PONV 1*	0[0-1]	0 [0-2]	.645
PONV-2*	1 [0-2]	2 [0-2]	0.912

After analyzing the blood pressure and pulse values between the groups, no statistically significant difference was observed in any measurement (Figure 1).

The measurement of pain in patients who had postoperative analgesia with ketoprofen is shown in Figure 2. Although patients with suggestive preparation had a lower VAS score in all measurements at rest, the difference was not statistically significant in any measurement.

The VAS scores during movement are presented in Figure 3. As at rest, the VAS scores were lower in all measurements in the group that had suggestive preparation, and the difference was statistically significant at VAS2 measurement in the recovery room. VAS2 was 3 [2-5] versus 2 [0-3.75] in the NP and SP group, respectively (P=0.008).

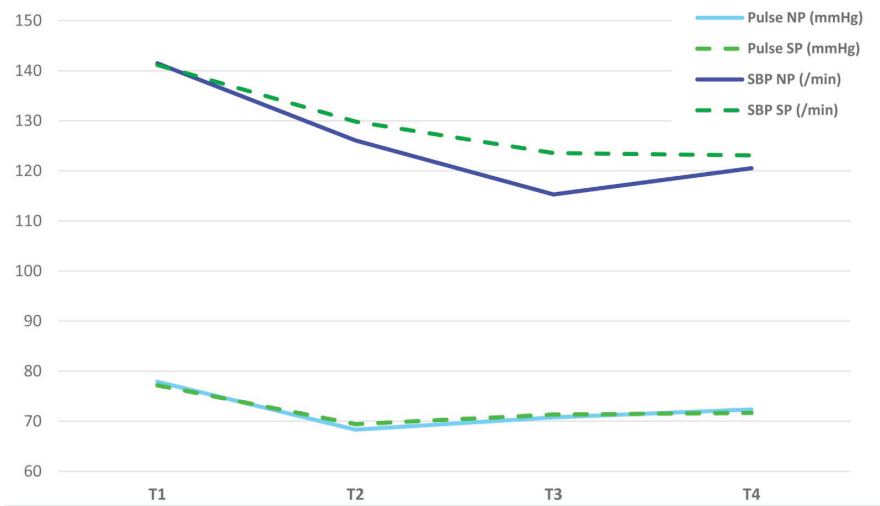

Figure 1. Systolic blood pressure measurements and pulse values registered immediately before anesthesia induction in the operating room (T1), after waking up in the recovery room (T2), 6 hours after the surgery at the surgical ward (T3) and on the morning after surgery in the surgical ward (T4) in the patients with no preparation (NP group) and with suggestive preparation (SP group).

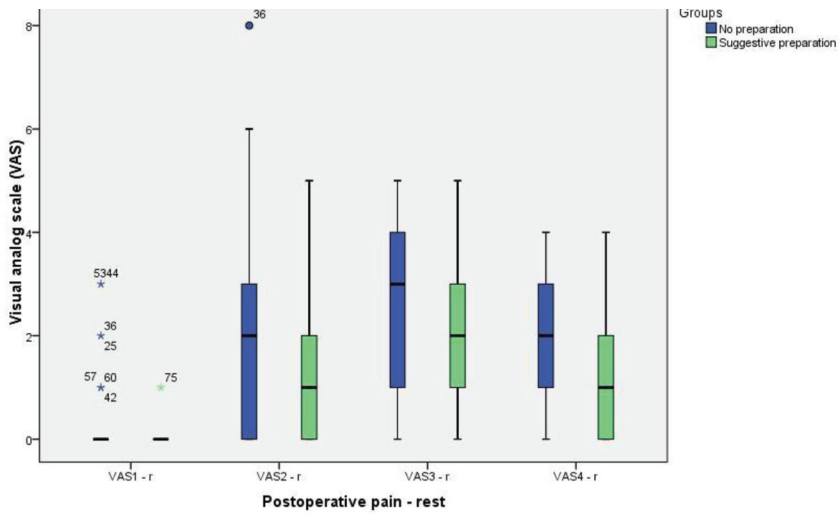

Figure 2. Postoperative pain at rest in patients after elective surgical procedures at rest. VAS scores were registered immediately before anesthesia induction in the operating room (VAS1), after waking up in the recovery room (VAS2), 6 hours after the surgery at the surgical ward (VAS3) and on the morning after surgery in the surgical ward (VAS4) in patients with no preparation (NP group) and with suggestive preparation (SP group).

In our study group, female patients had lower blood pressure at T1 (138 [122-146] mmHg vs. 145 [129.75-155] mmHg, P=0.030) and at T3 (120 [108-120] vs.125 [115-0] mmHg in female and male patients respectively, P=0.010). Pain scores were different in female in comparison with male patients at VAS3r measurement. VAS3r was 3 [1-4] in women vs. 2 [1-3] in male patients (P=0.03). Pain scores were higher in female patients at VAS3m (5 [3-5] in female vs. 3 [3-4] in male patients, P=0.017), and VAS4M (4 [3-4] in female vs. 3 [2-4] in male patients, P=0.041). Female patients had more PONV (r=0.449, P<0.001).

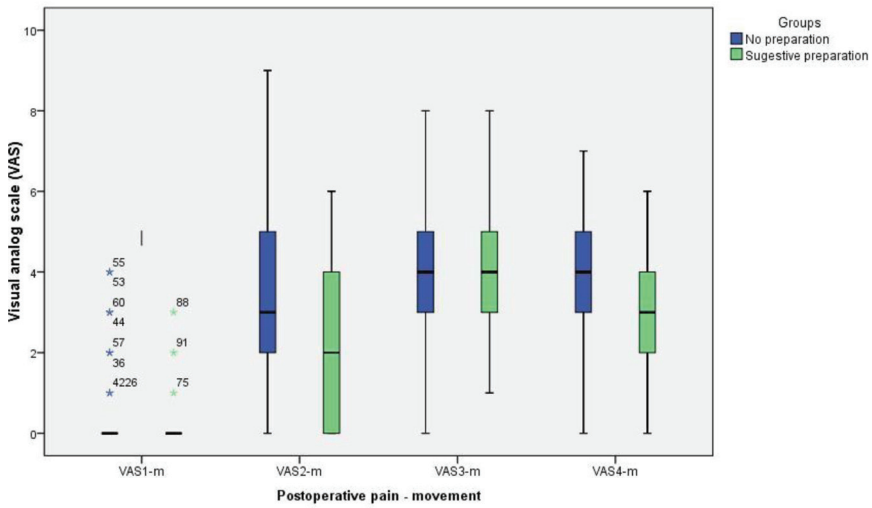

Figure 3. Postoperative pain during movement in elective surgical patients during 24 postoperative hours.

There was a correlation between hypertension and VAS1 at rest (r=0.353, P=.002) and in movement (r=0.305, P=0.007). Despite receiving medications, blood pressure measurements were higher in hypertensive patients at T1 and T4 measurement (138 [124.25-149.25] vs. 150 [136.25 vs. 156.75] mmHg at T1 and 120 [110-130] vs. 120 [120-137.5] mmHg in normotensive and hypertensive patients, respectively, P<0.05 for both). Non-hypertensive patients had lower pain scores at T1 at rest (0 [0-0] vs. 0 [0-0.5], P=0.006) and in movement (0 [0-0] vs 0 [0-1]; P=0.019). VAS4 score was in the correlation with BMI (r=0.268, P=0.026). Other comorbidities were not in the correlation with pain or postoperative PONV.

Postoperative opioid use decreased with patient age (r=-0.533, P=0.033). It was in correlation with the intensity of postoperative nausea and vomiting (r=0.009, P=0.003) and with female gender (R=0.438, P<0.001). Postoperative opioid use was registered in a total of 23 (52%) male patients and 22 (67%) women due to the VAS scores ≥4, (ns, P=0.204).

Discussion

The results of our study demonstrated that ketoprofen was effective for postoperative pain relief in patients undergoing moderate invasive abdominal surgery. The pain scores were significantly higher during movement than at rest, just as was observed by Cachemaille et al[7]. In their study, pain scores and risk factors for acute postoperative pain after various abdominal surgery procedures were analyzed. Among other results, they concluded that younger age correlates with high opioid consumption and high pain scores[7], just as observed in our study. A multimodal approach to the treatment of acute postoperative pain is a method to reduce postoperative pain and opioid consumption. In our study, the multimodal approach included suggestive preparation, the use of NSAIDs and the adjusted use of opioids, according to the severity of acute pain. With suggestive preparation, lower postoperative consumption of opioids was achieved, although it was not statistically significant in this number of patients.

The VAS scores in all measurements at rest and during movement were lower in the SP group, but the difference was statistically significant at the VAS 2 measurement in the recovery room. The effect of the suggestion on pain reduction was time-limited to the period in which the patients remembered the instructions they received, which was also observed in an earlier neurophysiological study by the Petrovic et al[8].

Comorbidity is often associated with pain perception. In our study, we observed a correlation between hypertension and higher VAS scores. Hypertensive patients had higher blood pressure measurements despite continuing their antihypertensive therapy in the perioperative course, and consequently had increased VAS scores. The systolic BP measurements in our study did not differ between the NP group and SP group throughout the 24-hour observation period.

The relationship between pain and hypertension is potentially of great pathophysiological and clinical interest, but still is poorly understood[9]. Sacco et al. analyzed the relationship between blood pressure and pain and found that the degree of pain correlated with the increase in blood pressure and vascular resistance. The authors believe that hypertensive patients more often develop a condition known as "hypertension-associated hypoalgesia", which was not observed in our study. The authors believe that this condition is typically observed in myocardial ischemia, when there is no adequate pain accompanying high pressure to serve as a warning sign. This explains why silent myocardial ischemia is twice as common in hypertensive patients than in normotensive patients[10].

The results of our study showed that the VAS score was in significant correlation with body mass index (BMI). Patients with higher BMI had higher VAS scores. Observations on the relationship between pain and BMI in the literature are different[11]. Gonzalez-Callejas et al. analyzed postoperative pain eight hours after inguinal hernioplasty. In a study involving 99 patients, they did not confirm that BMI was associated with postoperative pain[12]. In contrast, Zengin et al. found a positive correlation between BMI and VAS scores in thoracotomy patients with postoperative thoracic epidural analgesia. This correlation was supported by the increased need for additional analgesics in patients with high BMI[13]. The observed correlation between increased subjective pain and higher BMI may be related to the volume of distribution of drugs. Therefore, in overweight patients, liposoluble opioids that have a three-compartment distribution can accumulate in lipids and should be carefully titrated[14]. In contrast, ketoprofen has a two-compartment pharmacodynamic that is essentially weight-independent[15]. In case of unsuccessful pain control after an adjusted dose of ketoprofen, it should not be increased, but rescue medication should be given instead.

As expected, our results showed that patients with higher opioid consumption and female gender tended to have a higher incidence of postoperative nausea and vomiting. Torres et al. evaluated the correlation between gender, age, BMI values and the severity of postoperative pain and PONV in patients undergoing laparoscopic cholecystectomy[11]. They found that female gender was a risk factor for PONV, and registered a positive relationship between BMI and postoperative pain, as in our study. Based on the results of their study, patients with high BMI should have better preoperative evaluation, including preoperative endocrinological diagnostics, employ dietician consultations and should employ careful dosing and choice of anesthetics and analgesics.

The present study had some weaknesses. As a prospective and randomized study, both patients who underwent cholecystectomy and hernioplasty were included. We compared pain in these two categories because both procedures are considered moderately invasive procedures according to surgical complexity[16]. Furthermore, the study was conducted on a relatively small number of patients, and statistical significance was not achieved for VAS in most measurements, although differences were present. Patient satisfaction with postoperative analgesia, which may be significantly influenced by suggestion, was not examined. A future prospective and randomized study with a larger number of study parameters could provide more data on the effects of suggestive preparation in postoperative pain management.

Conclusions

Communicating with patients prior to the procedure is a key element in preparation for surgery. Effective communication and clarity of information exchange is essential for quality of care, patient safety and better clinical outcomes. Suggestive preparation can help with the patient's acceptance of pain treatment. Special attention is needed to improve pain control in hypertensive and obese patients, particularly at mobilization.

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Sažetak

SUGESTIVNA PRIPREMA PACIJENATA PRIMJENOM INTRAVENSKOG KETOPROFENA KAO DIO POSTOPERATIVNOG LIJEČENJA BOLI NAKON KIRURŠKE OPERACIJE TRBUHA

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Sugestivna priprema prije operacije može imati placebo učinak i smanjiti perioperativnu potrošnju analgetika. Ukupno 77 odraslih pacijenata podvrgnutih elektivnoj kolecistektomiji i hernioplastici bilo je uključeno u prospektivnu studiju. Svi pacijenti su dobili 100 mg ketoprofena intravenski i podijeljeni su u dvije skupine. Prva skupina nije bila informirana o analgeziji (bez pripreme, NP skupina), a drugoj skupini rečeno je da će dobiti jaki lijek protiv bolova (sugestivna priprema, SP). Puls, krvni tlak i VAS zbrojevi su registrirani kod svih pacijenata neposredno prije uvođenja u anesteziju u operacijskoj sali (T1), nakon buđenja u sobi za oporavak (T2), 6 sati nakon operacije na kirurškom odjelu (T3) i u jutro nakon operacije na kirurškom odjelu (T4) u mirovanju i tijekom kretanja. Dodatni nesteroidni analgetici ponuđeni su pacijentima s VAS 3-4, a opioidi za VAS ≥ 5. Bolesnici u SP skupini imali su niže VAS rezultate u svim mjerenjima i manju potrošnju opioida. Statistički značajna razlika bila je u mjerenju VAS2 u pokretu (3 [2-5] naspram 2 [0-3,75] u NP i SP skupini, P=0,008). SP je imala placebo učinak, smanjila VAS kao i potrošnju opoida.

Ključne riječi: *placebo učinak; sugestija; ketoprofen; akutna postoperativna bol; vizualna analogna ljestvica.*