

# ANALGESIC EFFECT – COMPARISON OF PARACETAMOL ADMINISTERED INTERMITTENTLY AND THROUGH PATIENT-CONTROLLED ANALGESIA PUMP AFTER LUMBAR DISCECTOMY: A PROSPECTIVE CLINICAL STUDY

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**SUMMARY** – Lumbar discectomy is the most common surgical treatment for intervertebral disc extrusion. Postoperative pain is a common clinical problem that greatly affects the length of hospitalization, functional status and patient quality of life. The aim of this study was to compare the postoperative analgesic efficacy of paracetamol administered intermittently and through patient-controlled analgesia (PCA) pump following single level lumbar discectomy. Patients who underwent elective lumbar discectomy of intervertebral disc extrusion at the L4-L5 level diagnosed by magnetic resonance of the lumbosacral spine were included in the study. Pain was assessed at regular intervals for 48 hours through a shortened version of McGill pain questionnaire translated in the Croatian language. When pain was monitored as a summarized variable for each measurement, PCA group significantly stood up after 24 hours with better perception of pain compared to the intermittent group ( $\chi^2$ -test,  $p < 0.05$ ). Adequate pain relief is an important aspect of postoperative care in spinal surgery patients. Postoperative use of paracetamol through PCA pump achieved better pain control and pain management *versus* postoperative use of intermittent paracetamol analgesia after lumbar discectomy.

**Key words:** *Acetaminophen; Pain, postoperative – drug therapy; Analgesics – therapeutic use; Discectomy; Croatia*

## Introduction

Inadequate pain treatment has negative effects on patient postoperative recovery. Despite progress in the pathophysiology and management of pain, availability of new drugs and complex drug delivery systems, the postoperative pain treatment of many patients remains deficient<sup>1</sup>. Postoperative pain is associated with de-

creased patient satisfaction, delayed postoperative ambulation, increased risk of pulmonary and cardiac complications, and increased morbidity and mortality<sup>2-7</sup>. Inadequately treated pain can cause additional stress, which can affect the immune system and result in delayed healing, and may be a trigger for the chronic pain syndrome<sup>8,9</sup>. The goal of postoperative pain treatment is to ensure that organ functioning returns to normal by controlling pain as soon as possible<sup>3</sup>.

In a recent study of 179 surgical procedures, spinal surgery procedures ranked among the top six interventions that cause most postoperative pain<sup>2</sup>. The most commonly performed spinal surgical procedure is sin-

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Received March 24, 2017, accepted May 11, 2017

gle level lumbar interlaminectomy with discectomy. It involves dissection of the skin, subcutaneous tissue, lumbar fascia and muscles, ligamentum flavum, occasionally some amount of vertebral lamina and lumbar disc. Postoperative pain is the result of activation of various pain mechanisms including nociceptive, neuropathic and inflammatory mechanisms<sup>10,11</sup>. The pain after discectomy is severe and typically lasts for three days<sup>12</sup>. It is directly proportional to the number of levels involved and is similar in surgeries of cervical, thoracic and lumbar region<sup>13-16</sup>.

Postoperative pain is transitory and gradually improves making it more amenable to medical therapy in comparison to chronic pain<sup>17</sup>. Therefore, adequate pain relief is a very important aspect of early postoperative care. Sharma *et al.* state that there are several strategies that are used for pain relief after lumbar discectomy, but there is a lack of systematic analgesic treatment documentation in this patient population<sup>18</sup>. Successful postoperative analgesia may be achieved by selecting appropriate drug, drug dosage and administration route. Opioid analgesics are the most widely used drugs but carry unpleasant side effects<sup>19</sup>. Nonsteroidal anti-inflammatory drugs (NSAIDs) have proven efficacy in ameliorating postoperative pain, especially following spinal surgery<sup>20-22</sup>. Side effects such as gastric irritation, inhibition of platelet aggregation and bleeding have restricted their wide use<sup>23</sup>.

Paracetamol is one of the nonselective cyclooxygenase inhibitors, acting by inhibiting the synthesis of prostaglandins and other substances that sensitize pain receptors in the central nervous system and periphery<sup>24</sup>. This drug is an efficacious analgesic agent and has no side effects that are observable with opioids or NSAIDs<sup>25</sup>. The intravenous form of paracetamol is a suitable drug in the treatment of mild and moderate postoperative pain and can be administered intermittently or by patient-controlled analgesia (PCA) pump.

Patient-controlled analgesia is a pain control method that allows patients to independently apply analgesic doses by computerized pumps. PCA has been proven as very effective in the treatment because it is tailored to patient needs<sup>26</sup>.

This study was designed to compare postoperative analgesic efficacy of paracetamol administered intermittently and through PCA pump after single level lumbar discectomy.

## Materials and Methods

Following institutional ethics board approval and signed written informed consent, 56 patients aged 27-80, classified as American Society of Anesthesiologists (ASA) I and II, scheduled for elective lumbar discectomy of intervertebral disc extrusion at the L4-L5 level, participated in the study. Preoperative exclusion criteria were surgery performed under regional anesthesia, contraindications to NSAIDs, and age less than 18 or more than 85 years, ASA  $\geq$ III, emergency neurosurgical procedure due to neurological deficit, recurrent surgery, patients with a history of chronic liver diseases, existence of malignant disease, patients allergic to analgesics, patients with a history of drug abuse, patients under immunosuppressive therapy, patients with mental incapability to give informed consent, inability to use PCA pump, and patients with communication difficulties. Postoperative exclusion criteria included difficulty with the use of PCA pump and postoperative prescription of other analgesic drugs.

On the day before lumbar discectomy, patients were informed about the undergoing study, prospective drug, PCA device, and shortened version of McGill pain questionnaire. All patients were administered dalteparin sodium (Fragmin) by subcutaneous injection and diazepam (Normabel) orally at 10 pm the night before surgery. On the day of surgery, midazolam (Dormicum) and atropine intramuscular were administered at 8 am as routine premedication. Doses of preoperative medications were tailored according to patient age and weight individually.

The induction of general anesthesia was achieved with propofol (1.5-2.5 mg/kg), sufentanil (0.3 mcg/kg) and vecuronium (0.1 mg/kg) bolus dose and maintained with sevoflurane, 50%/50% O<sub>2</sub>-air. Sufentanil was supplemented throughout surgical procedure according to patient anesthetic situation.

The study was planned as a randomized prospective study. Randomization was performed with the MedCalc for Windows, version 15.1 ([www.medcalc.be](http://www.medcalc.be)) statistical software. There were two groups of study participants: INTER group (intermittent application group), administered first paracetamol dose of 1500 mg in the operating room upon completion of the neurosurgical procedure and 1500 mg every 6 hours for 48 hours (n=32). Patients in the PCA group (PCA pump group) were administered first bolus dose of paracetamol (166 mg) in the operating room upon completion of the neurosurgical procedure, with lockout time bolus adminis-

Table 1. Sociodemographic variables

		Group				p
		INTER		PCA		
		n	%	n	%	
Age (years)	≤35	5	15.6	6	25.0	0.573
	35-45	11	34.4	9	37.5	
	45-55	3	9.4	4	16.7	
	55-65	8	25.0	3	12.5	
	>65	5	15.6	2	8.3	
Gender	Male	12	37.5	12	50.0	0.35
	Female	20	62.5	12	50.0	
Work status	Unemployed	5	15.6	2	8.3	0.716
	Moderate work	16	50.0	13	54.2	
	Hard work	11	34.4	9	37.5	
Education	Elementary school	3	9.4	4	16.7	0.292
	High school	19	59.4	16	66.7	
	Undergraduate	4	12.5	0	0.0	
	Graduate	6	18.8	4	16.7	
Physical activity	No	0	0.0	4	16.7	0.017
	Yes	32	100.0	20	83.3	
Smoking	No	18	58.1	15	62.5	0.739
	Yes	13	41.9	9	37.5	

INTER = intermittent paracetamol; PCA = patient-controlled analgesia

tration at 120 minutes and basal flow rate of 16.6 mL/h for 48 hours (n=24). Paracetamol has an analgesic effect that starts within 0.5 to 1 hour and lasts for 6 to 8 hours. This is consistent with the plasma half-life of 2.7 hours. The elimination half-life is 1 to 4 hours and it can be used as 1-g infusion<sup>9</sup>.

Pain was evaluated at regular time intervals (7 pm, 7 am, 7 pm, 7 am and 7 pm) through the shortened version of McGill pain questionnaire, in Croatian language, for 48 hours postoperatively.

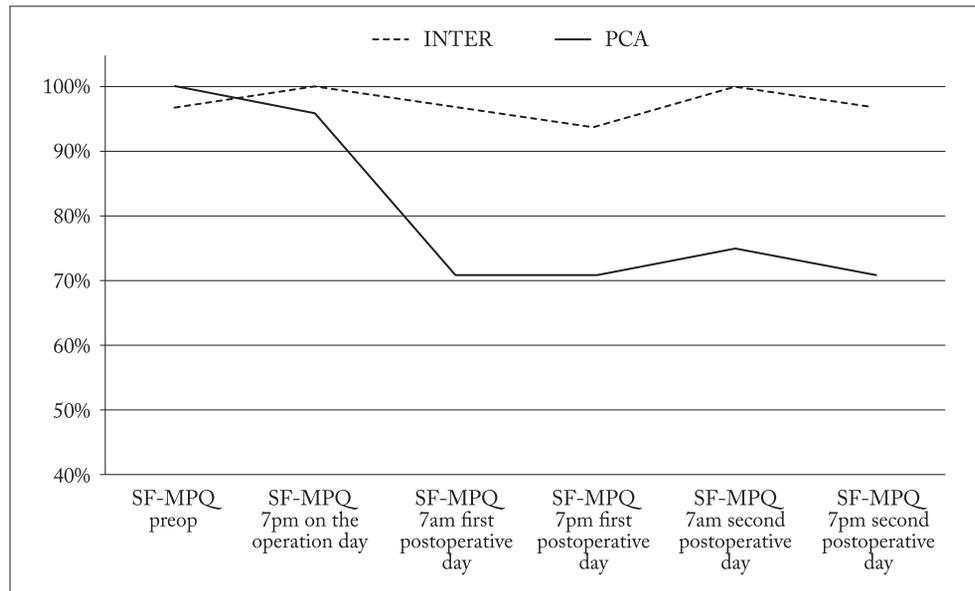
Statistical analysis was performed using StatsDirect version 3.1.1. The  $\chi^2$ -test was used to compare qualitative data. To assess the impact of paracetamol received intermittently or through PCA pump, binary logistic regression was performed. The level of statistical significance was set at  $p < 0.05$ .

## Results

There was no statistically significant difference between the study groups according to sociodemograph-

ic data, except for physical activity. Participants from the INTER group were significantly more physically active prior to surgery (100.0% *vs.* 83.3%;  $p = 0.017$ ) (Table 1).

Pain severity before surgery, as measured by McGill pain questionnaire, was described as distressing by 48.4% of INTER group patients and 58.3% of PCA group patients. After lumbar discectomy, pain was assessed at 7 pm on the day of surgery in both groups, and there was no significant difference between them. On the first postoperative day, a statistically significant difference in terms of pain relief was noticed in PCA group (7 am: 41.7%, 7 pm: 41.7%) *versus* INTER group (7 am: 67.7%, 7 pm: 71.9%;  $\chi^2$ -test,  $p < 0.05$ ). PCA group showed significantly better pain relief on the second postoperative day, i.e. at 7 am 25% of patients experienced no pain, whereas in INTER group at the same time interval 0% of patients experienced total pain relief. At 7 pm on the second postoperative day, both groups showed better paracetamol analgesia effect in terms of better pain relief. Pain relief was sta-



INTER = intermittent paracetamol; PCA = patient-controlled analgesia

Fig. 1. Differences in pain perception between study groups.

tistically significant in PCA group *versus* INTER group (no pain, 29.2% *vs.* 3.1%;  $p < 0.001$ ) (Fig. 1).

When pain was monitored as summarized variable for each measurement, PCA group significantly stood up 24 hours after surgery with ameliorated pain perception as compared with INTER group ( $\chi^2$ -test,  $p < 0.05$ ) (Table 2).

## Discussion

Efficacious pain management is mandatory for appropriate postoperative recovery. There are differences in the efficacy of analgesics according to pain type, pain location and methods of pain relief. Studies of analgesic efficacy of various drugs are necessary and important<sup>24</sup>. However, trial data on analgesic therapy after spinal surgery are limited, and there are great differences in management practices. Spinal procedures are generally associated with intense pain in the postoperative period, especially in the first few days. The preexisting pain along with long-term consumption of analgesics alters pain perception in these patients, thereby complicating postoperative pain management<sup>27,28</sup>. Adequate pain management in this period has been observed to correlate well with improved functional outcome, early discharge, better ambulation, and preventing development of chronic pain syn-

drome<sup>2</sup>. Although opioid analgesics are the most widely used drugs for controlling postoperative pain, some authors have emphasized the use of intravenous paracetamol to improve postoperative pain and increase patient satisfaction following this type of surgery<sup>29-32</sup>. The efficacy of paracetamol alone in the treatment of mild-to-moderate postoperative pain and its place in combination treatment were investigated<sup>33-35</sup>. Studies of combination treatment have shown that paracetamol has an opioid reducing effect and that it significantly reduces patient need for total opioids, thus increasing patient overall satisfaction with analgesic therapy<sup>33,36</sup>. Our study compared the analgesic effect of intravenous paracetamol alone when administered intermittently and using PCA device after single level lumbar discectomy. In the current study, patients in both groups had satisfactory pain control results, especially on the second postoperative day.

Paracetamol is the preferred analgesic in the treatment of postoperative mild and moderate pain. The onset of analgesia begins within 5-10 min of intravenous paracetamol administration. The mechanisms of paracetamol action have not yet been fully understood and may involve inhibition of central cyclooxygenase (COX-3) pathway in the central nervous system and interaction with the serotonergic system<sup>37</sup>. Intravenous paracetamol is a fast-acting analgesic and is more

Table 2. Pain severity before surgery and within 48 hours after lumbar discectomy

		Group				p
		INTER		PCA		
		n	%	n	%	
Question No. 1: upon patient admission for hospitalization, prior to surgery	No pain	1	3.2	0	0.0	0.151
	Mild	2	6.5	1	4.2	
	Discomforting	5	16.1	8	33.3	
	Distressing	15	48.4	14	58.3	
	Horrible	8	25.8	1	4.2	
Question No. 2: 7 pm on the operation day	No pain	0	0.0	1	4.2	0.473
	Mild	17	54.8	16	66.7	
	Discomforting	12	38.7	6	25.0	
	Distressing	2	6.5	1	4.2	
	Horrible	0	0.0	0	0.0	
Question No. 3: 7 am first postoperative day	No pain	1	3.2	7	29.2	0.048
	Mild	21	67.7	10	41.7	
	Discomforting	8	25.8	6	25.0	
	Distressing	1	3.2	1	4.2	
	Horrible	0	0.0	0	0.0	
Question No. 4: 7 pm first postoperative day	No pain	2	6.3	7	29.2	0.046
	Mild	23	71.9	10	41.7	
	Discomforting	7	21.9	6	25.0	
	Distressing	0	0.0	1	4.2	
	Horrible	0	0.0	0	0.0	
Question No. 5: 7 am second postoperative day	No pain	0	0.0	6	25.0	0.007
	Mild	28	87.5	12	50.0	
	Discomforting	3	9.4	5	20.8	
	Distressing	1	3.1	1	4.2	
	Horrible	0	0.0	0	0.0	
Question No. 6: 7 pm second postoperative day	No pain	1	3.1	7	29.2	0.012
	Mild	28	87.5	12	50.0	
	Discomforting	1	3.1	3	12.5	
	Distressing	2	6.3	2	8.3	
	Horrible	0	0.0	0	0.0	

INTER = intermittent paracetamol; PCA = patient-controlled analgesia

effective in terms of analgesia onset than oral paracetamol. Piguet *et al.* demonstrated in healthy volunteers that the analgesic effect and plasma concentration of paracetamol were closely correlated and were dose-dependent, concluding that intravenous paracetamol had a dose-dependent central nociceptive ef-

fect<sup>38</sup>. Juhl *et al.* demonstrated that the analgesic efficacy of a 2-g starting dose of intravenous paracetamol was superior to the recommended dose of 1 g in terms of the magnitude and duration of analgesic effect<sup>39</sup>. In our study, 6 g/day of intravenous paracetamol was administered intermittently and *via* PCA pump with

similar results concerning pain control, especially on the day of surgery.

Despite a low incidence of adverse effects, paracetamol has a recognized potential for hepatotoxicity, platelet function inhibition and bleeding<sup>23</sup>. Patients with chronic liver disease and history of drug abuse were excluded from the study. In patients on anticoagulation therapy, the international normalized ratio (INR) was closely monitored due to the paracetamol effect on increasing the INR<sup>40</sup>. Although there are side effects reported with the use of paracetamol, none was recorded in our study.

Studies by Grundmann *et al.* and Lin *et al.* showed paracetamol to be an analgesic with few side effects, wide dosage range and easy use<sup>41,42</sup>. Cakan *et al.* studied the efficacy of paracetamol following lumbar disc surgery and concluded that paracetamol decreased visual analog scale (VAS) scores but did not decrease morphine consumption<sup>29</sup>.

The hypothesis in our study was that intravenous paracetamol, administered through intermittent use or PCA pump, could relieve postoperative pain in patients undergoing lumbar discectomy. We found a significant difference in terms of pain control on the first and second postoperative day in favor of PCA administered paracetamol group. Postoperative use of paracetamol analgesia through PCA pump achieved better pain control and pain management *versus* postoperative use of intermittent paracetamol analgesia after lumbar discectomy.

Our results are in concordance with the studies by Yilmaz *et al.* and Cakan *et al.*, although they combined paracetamol with tramadol and morphine<sup>24,29</sup>. Despite the more effective control of postoperative pain by opioid analgesics, paracetamol alone may be considered as an efficacious analgesic for postoperative pain relief following lumbar disc surgery.

The present study had some limitations, particularly considering the small number of participants and short time of pain evaluation (48 hours). Although multimodal analgesia is the recommended strategy for postoperative analgesia, there is no consensus on the appropriate multimodal analgesia protocols or algorithms<sup>43</sup>. Further studies should be directed towards conducting functional analgesic treatment that will reflect the appropriate effects of pain relief strategies.

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## Sažetak

## USPOREDBA ANALGETSKOG UČINKA PARACETAMOLA PRIMIJENJENOG INTERMITENTNO I PUTEV SAMOSTALNO KONTROLIRANE CRPKE NAKON LUMBALNE DISKEKTOMIJE: PROSPEKTIVNA KLINIČKA STUDIJA

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Lumbalna diskektomija je najčešći kirurški način liječenja hernijacije intervertebralnog diska lumbalnog dijela kralježnice. Bol je čest klinički problem koji uvelike utječe na trajanje bolničkog liječenja, funkcionalni status i kvalitetu života bolesnika. Cilj studije bio je usporediti učinkovitost poslijeoperacijske analgezije paracetamolom primijenjenim intermitentno i putem samostalno kontrolirane crpke (*patient-controlled analgesia*, PCA) nakon neurokirurškog operativnog zahvata ekstruzije intervertebralnog diska na razini L4-L5. Ispitanici su bili bolesnici kojima je elektivnim zahvatom učinjena lumbalna diskektomija intervertebralnog diska na razini L4-L5, ustanovljena magnetskom rezonancom. Bol je procjenjivana u jednakim vremenskim intervalima kroz 48 sati putem skraćene verzije McGillova upitnika za procjenu boli, na hrvatskom jeziku. Promatrajući bol kao sažetu varijablu svakog mjerenja, skupina ispitanika PCA je pokazala značajno bolje rezultate percepcije boli nakon 24 sata od operacijskog zahvata u odnosu na skupinu koja je primala intermitentno primijenjenu analgeziju paracetamolom ( $\chi^2$ -test,  $p < 0,05$ ). Odgovarajuća poslijeoperacijska analgezija važan je aspekt poslijeoperacijske skrbi bolesnika nakon kirurškog zahvata na kralježnici. Poslijeoperacijska primjena paracetamola putem PCA dovodi do bolje kontrole boli u usporedbi s intermitentnim davanjem paracetamola u bolesnika nakon lumbalne diskektomije.

Ključne riječi: *Acetaminofen; Bol, poslijeoperacijska – farmakoterapija; Analgetici – terapijska primjena; Diskektomija; Hrvatska*