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Efficacy and safety of intravenous paracetamol in the early postoperative period after minor surgical interventions

The problem of pain remains one of the global and unresolved issues in modern medicine. Each surgical intervention is accompanied by an intended surgical injury, the elimination of the consequences of which is the main task of the postoperative period [1].

At the IV Congress of European Pain Associations (Prague, September 2003), it was noted that at least 35% of patients, who underwent scheduled and emergency surgical interventions, suffered from postoperative pain. In one of the largest studies (about 20,000 patients in the UK surgical departments), postoperative pain sensations of moderate intensity were recorded in 29.7% of cases (26.4-33%), high intensity in 10.9% of cases (8.4%-13.4%) (Dolin S., Cashman J., 2002).

Unresolved pain in the early postoperative period, except for expressed subjective discomfort, is fraught with a number of serious complications that can become a serious obstacle to the recovery of the patient. Control of postoperative pain allows to reduce the risk of serious postoperative complications: ischemia and myocardial infarction, tachycardias, arrhythmias, atelectasis, thromboembolic complications, peripheral vasoconstriction, metabolic acidosis, and disturbances in the healing process of a postoperative wound [1, 2].

Adequate relief of postoperative pain provides the best level of recovery, improved patient comfort (decreased psychological stress, increased motivation to recovery and early mobilization), reduced impact of stress on the cardiovascular system, reduced number of pulmonary and thromboembolic disorders, motility disorders of digestive tract, urine retention, immunological disorders, septic complications, mortality in high-risk patients, chronic neuropathic pain, as well as a decrease in medical costs [1, 2].

In most developed countries, postoperative analgesia is carried out in accordance with accepted national and international standards. For some reasons, they can not be fully adopted in Ukraine (due to the lack of a clear regulatory framework; the orders restricting the prescription of opioid analgesics; the lack of permission for the use of certain drugs; the lack of extensive use of the methods of patient-controlled analgesia, etc.). Nevertheless, international recommendations, in particular, Acute Pain Management: Scientific Evidence (2005), summarizing the evidence-based medicine data on the efficacy of various agents and methods of postoperative analgesia, as well as guidance Postoperative Pain Management – Good Clinical Practice (2005), may be followed to a certain extent.

Currently, a formulary system for the use of therapeutic drugs of certain groups, the suitability of which is confirmed by evidence-based medicine data, as well as caused by the needs and peculiarities of a particular medical institution, have been introduced in many clinics. All surgical units, as well as the departments of anesthesiology, resuscitation and intensive care, are believed to have only those analgesics and anesthetics, whose efficacy and safety have been confirmed by Level I Evidence (systematized reviews and materials) and Level II Evidence (randomized controlled trials with certain results) (Table 1) [3].

At present, there is no perfect analgesic or method of treatment for acute postoperative pain.

It is possible to approach to solving the problem of the adequacy of postoperative analgesia by implementing the concept of analgesia, which involves the simultaneous administration of two or more analgesics and/or methods of analgesia, having different mechanisms of action and allowing adequate analgesia with a minimum of side effects.

The selection of this or that regimen of analgesia is determined by the injurious nature of surgical intervention (Tables 2, 3).

Table 1. Drugs, the use of which for postoperative analgesia is supported by the evidence-based medicine data (Acute Pain Management: Scientific Evidence, 2ed, 2005)

Group	Drugs	Dose, route of administration
Non-opioid analgesics, non-steroidal anti-inflammatory drugs	Diclofenac Ketoprofen Ketorolac	75 mg (150 mg daily), i.m. 50 mg (200 mg daily), i.m. 30 mg (90 mg daily), i.m.
Non-opioid analgesics, other	Paracetamol	1 g (4 g daily), i.v. infusion for 15 minutes
Opioid analgesics, potent	Morphine Promedol	5-10 mg (50 mg daily), i.v., i.m. 20 mg (160 mg daily), i.v., i.m.
Opioid analgesics, weak	Tramadol	100 mg (400 mg daily), i.m., i.v.
Adjuvant drugs	Ketamine	0.15-0.25 mg/kg, i.v.
Local anesthetics	Lidocaine 2% Bupivacaine 0.25% and 0.5% Ropivacaine 0.2% and 0.75% and 1%	600 mg daily* 400 mg daily* 670 mg daily*

Note: * – infiltration of wound margins, intrapleural administration, prolonged blockade of peripheral nerves and plexuses, prolonged epidural anesthesia; i.m. – intramuscular, i.v. – intravenous.

Table 2. Injury-based classification of surgical interventions

Degree of injury		
Low	Moderate	High
Arthroscopic operations on the knee joint, laparoscopic cholecystectomy, endoscopic operations in gynecology, phlebectomy, herniotomy, operations on the thyroid gland	Open hysterectomy, extirpation of the uterus with appendages, open cholecystectomy, total hip arthroplasty, osteosynthesis in limb fractures, most maxillofacial operations	Operations on upper abdominal cavity, thoracotomy, aortic surgery, surgery with lumbotic access, hemicolectomy, rectal resection, radical cystoprostatectomy, total knee arthroplasty, limb amputation

Table 3. Variants of analgesia regimens based on the injury of surgical interventions [3]

Surgery	Before operation	During operation	After operation
Low injury	I.v. or i.m. NSAIDs 30-40 minutes before the operation	General anesthesia and / or regional (from infiltration to spinal)[1]	NSAIDs (i.m. ketorolac at 30 mg twice a day) + paracetamol 1 g as i.v. infusion for 15 minutes 2-3 times a day[2, 3]
Moderate injury	I.v. or i.m. NSAIDs 30-40 minutes before the operation	General anesthesia and / or regional (from the blockade of peripheral nerves and plexuses to the combined spinal epidural). Paracetamol at 1 g as i.v. infusion for 15 minutes before the end of the operation	NSAIDs (i.m. ketorolac at 30 mg 2-3 times a day) + paracetamol at 1 g as i.v. infusion for 15 minutes 3-4 times a day + opioid analgesic (i.m. or i.v. tramadol at 100 mg 2-3 times a day or i.m. promedol at 20 mg twice a day)
High injury	I.v. or i.m. NSAIDs 30-40 minutes before the operation	General anesthesia with mandatory use of regional (preferred epidural) as a component. Induction regimen of analgesia should include bolus of ketamine at 0.25 mg/kg[4]. Paracetamol at 1 g as i.v. infusion for 15 minutes 30 minutes before the end of the operation	Prolonged epidural analgesia (0.2% ropivacaine at a rate of 4-10 ml/h + fentanyl at 0.1-0.3 mg daily)[5] + paracetamol at 1 g as i.v. infusion for 15 minutes 2-3 times a day[6, 7, 8]

Note: NSAIDs – non-steroidal anti-inflammatory drugs, i.m. – intramuscular, i.v. – intravenous; [1] – epidural anesthesia is not indicated in low-injury surgery; [2] – NSAIDs and paracetamol are not recommended within >3 days of the postoperative period; [3] – combination of paracetamol with NSAIDs significantly improves the quality of analgesia (Level I Evidence, Acute Pain Management: Scientific Evidence, 2ed, 2005); [4] – bolus infusion of ketamine causes a clear opioid-saving effect that extends to the postoperative period (Fu E., 1997); [5] – ropivacaine and fentanyl are the drugs recommended by the European Association of Regional Anesthesia for long-term postoperative epidural analgesia (Postoperative Pain Management – Good Clinical Practice. General recommendations and principles for successful pain management, 2005); [6] – combination of EA and NSAIDs inhibits protein catabolism and reduces nitrogen losses in the early postoperative period (Asoh T., 1987); [7] – administration of NSAIDs does not increase the risk of epidural hematomas in patients who undergo EA (Bolivar M., 1999); [8] – basic analgesia with paracetamol and NSAIDs can reduce the rate of epidural infusion in patients with hypovolemia, i.e. avoid the development of a hypotension without loss of quality of analgesia.

Table 4. Number of patients who underwent a certain type of surgery

Type of surgery	Number of patients
Thyroidectomy	20
Knee joint arthroscopy	26
Laparoscopic cholecystectomy	16
Laparoscopy for gynecological diseases, as well as for infertility	18
Total	80

Given all the above information, it was difficult to miss the introduction of intravenous paracetamol at the Ukrainian market – the drug Infulgan (Yuria-Pharm Corporation). Paracetamol is an effective analgesic for the relief of acute pain; the rate of adverse events is comparable to that of placebo (Level I [Cochrane Review]). Intravenous paracetamol provides effective analgesia after surgical interventions (Sinatra et al., 2005, Level II). Its efficacy is comparable to that of ketorolac (Varrassi et al., 1999, Level II; Zhout et al., 2001, Level II), diclofenac (Hynes et al., 2006, Level II) and metamizol (Landwehr et al., 2005, Level II). In addition, it is not inferior to morphine in efficacy; however it has better tolerability in dental surgery (Van Aken et al., 2004, Level II). At comparable doses, paracetamol for intravenous administration is more effective and quick-acting than paracetamol for oral use [4].

The aim of the study is to determine the efficacy of the intravenous form of paracetamol for postoperative analgesia in minor surgical interventions as a monotherapy and in combination with NSAIDs.

Materials and methods

The course of the postoperative period during the first 6 hours after the surgery, as well as the intensity of the pain syndrome, was analyzed in 80 patients (Table 4).

The mean age of patients was 42 years. Risk on the ASA scale was I-II. Patients were divided into four groups (Table 5). Patients of all four groups received premedication 40 minutes prior to operation: 5 mg of sibazone and 1000 mg of analgin i.m.

Pain intensity was assessed using a visual analogue scale (VAS) (Figure). VAS is a straight line 10 cm long (100 mm). The starting point of the line indicates the absence of pain – 0, then goes weak, moderate, severe, terminal, intolerable pain – 10.

The patient was required to mark the pain level with a point on this straight line 30 minutes after the operation, in 3 hours and in 6 hours; the results are shown in Table 6.

Patients of group I, who had not received an analgesic 30 minutes before the end of the operation, required analgesia much earlier than patients from the other groups. Pain intensity was also much greater in patients of Group I. Injected 30 minutes before the end of the operation, dexketoprofen (Group II) and paracetamol (Group III) showed a similar degree of analgesic activity (60% [Group II], and 50% [Group III] of patients experienced minimum pain that did not require an analgesic after 30 minutes after awakening). In Group I already 30 minutes after the operation, 25% of patients experienced severe pain and only 15% had minimum pain. Group IV showed even better performance. In Group IV, patients did not need analgesics for the first 3 hours, and only two patients asked to perform analgesia 6 hours after the operation.

Table 5. Drug administration in study groups

Group I (n=20)	Group II (n=20)	Group III (n=20)	Group IV (n=20)
Placebo group, no NSAIDs	Received i.v. dexketoprofen at 50 mg 30 minutes before the end of the operation	Received i.v. drop infusion of paracetamol (Infulgan) at 1000 mg (100 ml) for 15 minutes 30 minutes before the end of the operation	Received i.v. drop infusion of paracetamol (Infulgan) at 1000 mg (100 ml) for 15 minutes + i.v. dexketoprofen at 50 mg 30 minutes before the end of the operation

Note: NSAIDs – non-steroidal anti-inflammatory drugs, i.m. – intramuscularly, i.v. – intravenous

Table 6. Pain intensity reported by the patients of I-IV groups

Group	In 30 minutes	In 3 hours	In 6 hours
Group I (n=20), placebo	Minimum: 3 (15%) Moderate: 12 (60%) Severe: 5 (25%)	Minimum: 0 Moderate: 13 (65%) Severe: 7 (35%)	Minimum: 0 Moderate: 9 (45%) Severe: 11 (55%)
Group II (n=20), dexketoprofen	Minimum: 12 (60%) Moderate: 7 (35%) Severe: 1 (5%)	Minimum: 8 (40%) Moderate: 10 (50%) Severe: 2 (10%)	Minimum: 3 (15%) Moderate: 13 (65%) Severe: 4 (20%)
Group III (n=20), paracetamol	Minimum: 11 (55%) Moderate: 8 (32%) Severe: 2 (18%)	Minimum: 8 (40%) Moderate: 9 (45%) Severe: 3 (12%)	Minimum: 2 (10%) Moderate: 14 (70%) Severe: 4 (20%)
Group IV (n=20), paracetamol + dexketoprofen	No pain: 5 (25%) Minimum: 12 (60%) Moderate: 3 (15%) Severe: 0	No pain: 4 (20%) Minimum: 12 (60%) Moderate: 4 (27%) Severe: 0	Minimum: 10 (50%) Moderate: 8 (40%) Severe: 2 (10%)

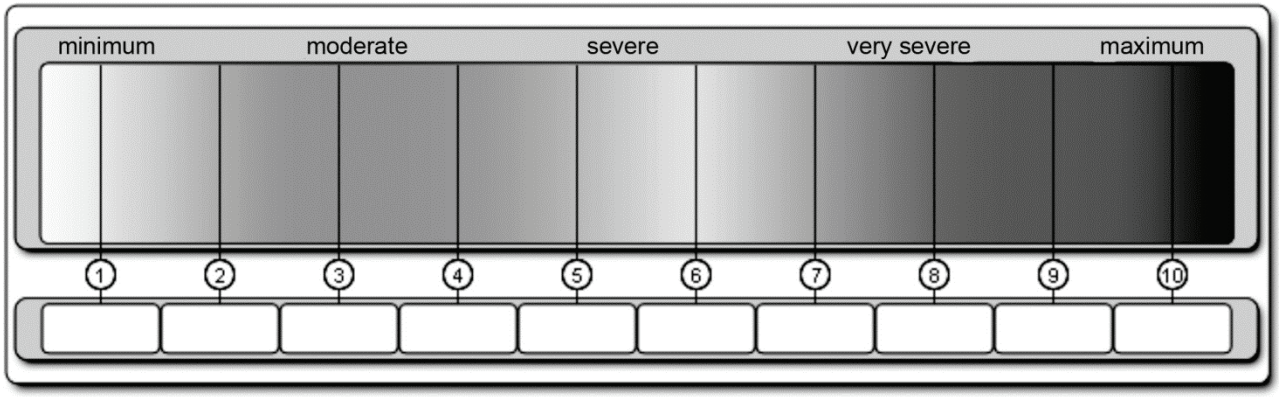

Figure. Visual-analogue scale of pain intensity

Conclusions

1. Paracetamol (Infulgan) or dexketoprofen, injected 30 minutes before the end of the operation, provides calm and painless awakening in most patients in minor surgical interventions.
2. Given the higher safety profile of paracetamol (Infulgan), it should be preferred in patients at high risk.
3. Combination of NSAIDs and paracetamol (Infulgan) improves the quality of analgesia. This combination is suitable due to the peculiarities of the impact on the mechanisms of pain – they complement each other; while the summation of analgesic efficacy is not accompanied by an increase in the number of side effects.

The use of the intravenous form of paracetamol (Infulgan) in minor surgical interventions allows to reduce the dose of opiate analgesics in the early postoperative period, as well as to improve the comfort of patient stay in the hospital.