Burianov O.A., DMedSc, Professor, Omelchenko T.M., Sobolevskyi Yu.L., Babochkin R.O.
National Medical University named after O.O. Bogomolets

Rational approaches to perioperative multimodal analgesia in orthopedic and trauma patients

Burianov O.A.

Analgesic therapy in patients with injuries and diseases of the musculoskeletal system is a complex, multicomponent problem that requires an individual approach to the specific pathogenetic mechanisms of pain and observation of the signs of efficacy, safety and adequacy of treatment. Undertreated acute pain has been shown to lead to chronization with the formation of an abnormal pain focus in the central nervous system (CNS). Post-traumatic pain syndrome is acute, nociceptive (somatogenic) and polymodal and includes somatic, visceral and neural components. This requires the use of the specified multimodal pharmacotherapy of the above pain syndrome to inhibit the afferent flow of pain impulsation at different levels of distribution.

The latter is provided by the use of different drug groups that affect different components of the nociceptive system. Local anesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotic analgesics, ketamine at subnarcotic doses and anticonvulsants belong to the drugs that are appropriate to include in the combined regimens of analgesia in patients with post-traumatic pain syndrome. The standard practice of the use of opiates and opioids in the existing technology is certainly effective, however causes the risk of such side effects as respiratory depression, inhibition of motility of the gastrointestinal tract, biliary tract and bladder. NSAIDs are also effective, but they are characterized by ulcerogenic potential, and even therapeutic doses can show ototoxicity, nephrotoxicity and hepatotoxicity. The use of anticonvulsants and local anesthetics for a guided regional anesthesia at various levels also has a number of limitations due to the possibility of adverse reactions.

Given the above, paracetamol, synthesized in 1878 and tested in the clinic in 1887 and widely used in medicine since 1950, is of considerable interest in terms of efficacy and safety of analgesia. Since 2001, paracetamol for intravenous administration is available in Europe under the trade name Perfalgan (Bristol Myers Squibb). Thence, a large number of clinical studies proved the high efficacy and safety of the use of Perfalgan as analgesic agent in various fields of medicine. In particular, the use of intravenous paracetamol in orthopedic patients is a subject of the studies conducted in 2005 and 2011 by R.S. Sinatra, J.S. Jahr, L.W. Reynolds, E.R. Viscusi and others. The authors reported the results of evaluation of analgesic effects of single and multiple intravenous paracetamol at 1000 mg in combination with morphine and compared to placebo for 24 hours in 101 patients with moderate to severe pain syndrome after orthopedic surgery. Patients, treated with paracetamol, experienced less pain and required less morphine (46% reduction within 6 hours and 33% reduction within 24 hours) compared with placebo. Analgesia satisfaction index was significantly higher in the intravenous paracetamol group: 79.6% of patients evaluated pain relief as excellent compared to 65.4% in the placebo group.

Today there is more new information on the mechanisms of action of paracetamol. The drug rapidly penetrates the blood-brain barrier, selectively inhibits COX 2 activity in CNS (prevention of secondary hyperalgesia) and activity of COX 3 (the existence of which is assumed and which probably has a selective sensitivity to paracetamol), enhances the activity of the downstream inhibitory serotonergic pathways. Paracetamol does not cause sedation, nausea, vomiting, and respiratory depression, and does not affect such important parameters as platelet aggregation and clotting time, has no ulcerogenic action. Introduction of parenteral paracetamol greatly expanded its indications and application in clinical practice as a basic drug for the perioperative multimodal analgesia.

In terms of safety, intravenous administration has significant advantages over the use of tablet forms due to better control of plasma concentration of the drug in the early postoperative period. This is supported by practical studies that found significant variations in the plasma paracetamol concentration in the early postoperative period up to dangerously high levels in the case of oral intake as opposed to intravenous administration. The main indications for paracetamol are pain and fever in pain syndrome.

In the surgical clinic, paracetamol is usually used in two ways. On the one hand, it can be administered as analgesic and antipyretic component of general inhalation or non-inhalation anesthesia. When using this technique, paracetamol at a dose of 1000 mg is administered as a premedicant or intravenous agent after induction during surgery in a patient with fever. Moreover, paracetamol at a dose of 1000 mg is administered intraoperatively approximately 30 minutes before the end of operation, which ensures a quiet and painless awakening. The absence of pain within the first 4-5 hours after surgery has a positive effect on further dynamics of the postoperative period.

Otherwise, analgesic and antipyretic effect of paracetamol is used in complex postoperative analgesia using adjuvant drugs (antihistamines, sedatives, hormones) in combination with other non-narcotic analgesics, including NSAIDs. Therewith, 1000 mg of paracetamol should be administered immediately after the transfer of the patient from the operating room to the resuscitation and intensive care unit and repeated every 4 hours (total dose 4 g/day). Administration of the drug is facilitated by the availability of finished dosage form that does not require dilution. After 1-3 days, intravenous paracetamol should be stopped and, if applicable, patients should be switched to the oral drug combined with other medicinal products.

Some experts consider paracetamol as an alternative to NSAIDs because their analgesic effect is comparable, however paracetamol is devoid of undesirable side effects specific to this class of non-steroidal analgesics (gastropathy, impaired hemocoagulation, leukopenia, etc.).

The view regarding high paracetamol hepatotoxicity is based on the data on suicidal paracetamol poisoning in the US. The use of maximum recommended daily dose of paracetamol for three consecutive days in patients suffering from alcoholism did not lead to an increase in serum transaminase levels and other markers of liver damage. Therefore, it can be stated that administration of paracetamol to patients with pain syndrome and fever for three days is safe. According to V.A. Peduto et al., the effect of therapeutic doses of paracetamol on the liver and kidney is similar to that of placebo.

Since 2012, paracetamol for intravenous administration under the trade name Infulgan manufactured by Yuria-Pharm is also available at the pharmaceutical market of Ukraine.

Introduction of this formulation opened the door to a significant enhancement of analgesia in patients of various categories, improvement of efficacy of analgesia and reduction of the rate of side effects, as evidenced by a significant increase in the number of publications by professionals in different spheres of medicine in Ukraine and near abroad.

Infulgan is available as a solution for infusion containing paracetamol 10 mg / 1 ml in vials of 20, 50 and 100 ml. The recommended maximum single dose is 1000 mg, the maximum daily dose is 4000 mg, and the interval between drug administrations should be at least 4 hours. Hypersensitivity to paracetamol and other components of the drug, and severe hepatocellular failure are the contraindications for the use of Infulgan. In pediatric practice, the drug is administered to children aged ≥1 year weighing >10 kg.

Efficacy and safety of Infulgan have been demonstrated in a prospective comparative study of perioperative analgesia in 49 patients with acute meniscal injuries of the knee joint and fractures of the bones of the ankle joint. The studies were conducted at clinical sites of the Department of Traumatology and Orthopedics of National Medical University named after O.O. Bogomolets. Patients were divided into clinical groups to compare the efficacy and safety of analgesia during the first three days after surgery.

In the treatment group, perioperative analgesia was performed according to recommended regimen as follows: intravenous paracetamol (Infulgan) was administered intraoperatively at 1000 mg approximately 30 minutes before the end of operation, and then, in the day of surgery, at 1,000 mg after 4-5 hours. On the second day, intravenous therapy was continued three times a day at intervals of 6 hours, and on the third day, the drug was administered up to 2 times as needed.

In the comparison group, analgesia was performed according to the classical technique using 1.0 ml of 2% solution of promedol twice a day in the first day after surgery, and on the second and third day, the drug was used once a day.

Starting form the second day, the same NSAIDs (dexketoprofen 50 mg/2 ml twice a day), antihistamines, sedatives, anticoagulants and other drugs were administered as adjuvants in both groups according to similar regimens. The treatment group consisted of 25 patients (17 females, 8 males), including 14 patients who underwent surgery for acute meniscal injury of the knee joint and 11 patients – for AO/ASIF type B bone fractures. The control group consisted of 24 patients (13 females, 11 males). 15 patients of this group received surgical treatment for acute meniscal injury, and 9 patients – stable functional osteosynthesis of the bones of the ankle joint. The methods of surgery and scope of operation in the groups were similar. The age distribution of the patients in the comparison group was the same; the age of patients ranged from 18 to 65 years (mean 42±18.7 years).

The efficacy of analgesia was assessed in all patients according to the following criteria:

- pain intensity on a visual analogue scale (VAS) in the first day after surgery, in two and three days;
- effect of the drug on general health of the patient;
- occurrence of side effects.

Follow-up of the patients in both groups was performed in the first, second and third day after surgery. Pain intensity on VAS, time of the first demand for analgesics, duration of analgesic therapy and analgesic effect were assessed (Table. 1). Assessment of pain intensity in the postoperative period was performed in the afternoon, allowing to determine the demand for narcotic analgesics. As previously stated, Infulgan was used in 25 patients of the treatment group. 24 patients of the comparison group received narcotic analgesics (promedol) for postoperative analgesia according to the above regimen. In addition, complex medical treatment in both groups included auxiliary drugs at conventional mean therapeutic doses according to similar regimens. The occurrence of side effects of paracetamol and narcotic analgesics and overall health of patients were recorded as well.

Evaluation of treatment using VAS (VAS, Huskisson) showed that the patients of the treatment group who received Infulgan intraoperatively, the average rate of pain intensity in the first three days after surgery were lower compared with that of opioids with a 95% degree of confidence, indicating statistical trend regarding this parameter.

Table 1. Mean parameters (M±m) of analgesia efficacy in the treatment (n_1=25) and comparison (n_2=24) groups in dynamics

Study parameters	Study groups		Type of surgery	
			Arthroscopic revision, meniscal resection	Open reduction, SF MIO of the shin bones
Pain intensity on VAS	1st day	Treatment	3.5±1.0	7.3±1.2
		Comparison	4.2±1.3**	8.6±1.6**
	2d day	Treatment	3.0±0.9	5.7±0.9
		Comparison	3.9±0.8**	6.2±1.2**
	3d day	Treatment	2.1±0.6	2.9±0.6
		Comparison	3.2±0.3*	3.9±0.3**
Time of the first demand for analgesic, h		Treatment	6.2±1.3	6.2±1.3
		Comparison	4.2±1.6*	2.3±0.8*
Duration of anesthesia, d		Treatment	0.8±0.7	2.8±0.9
		Comparison	1.7±1.1*	3.1±0.7***
Duration of pain relief, h		Treatment	5.9±1.4	4.5±1.2
		Comparison	5.2±1.7***	3.9±1.1***

Degree of significance of the difference with the parameter of the treatment group: *p<0.01; **p<0.05;***p>0.05

Table 2. Control of side effects during analgesic therapy during the first three days after surgery

Follow-up of study groups	1st day		2d day		3d day	
Control of side effects	Treatment	Control	Treatment	Control	Treatment	Control
	Number of cases in groups, n					
Dyspepsia, abdominal pain, nausea, constipation	3	5	1	4	-	2
Drowsiness	-	8	-	8	-	3
Headache	2	8	5	8	7	3
Disorientation	-	-	-	-	-	-
Dyspnea	-	-	-	-	-	-
Skin rashes	-	-	-	-	-	-
Swelling	-	-	-	-	-	-
Intoxication	-	-	-	-	-	-
Respiratory distress	-	-	-	-	-	-
Urinary retention	-	-	-	-	-	1

When comparing the time of the first demand for analgesia after surgery, a significant increase ($p < 0.01$) in the treatment group was observed both in minimally invasive arthroscopic interventions (6.2± 1.3 hours) and after surgery for fractures of the shin bones (4.2±1.4 hours), which proves the adequacy of analgesia initiated intraoperatively using parenteral paracetamol.

In addition, while performing arthroscopic interventions a significant ($p < 0.01$) decrease in the required duration of analgesia was reported in the treatment group compared with the control group. Patients who underwent metal osteosynthesis, a significant decrease in the duration of analgesia was not observed, and the total time of required postoperative analgesia was about three days.

The difference between the comparison groups in the duration of pain relief in arthroscopic surgery and metal osteosynthesis was not statistically significant ($p > 0.05$). This confirms the possibility of excluding the use of opioid analgesics and adequacy of intraoperative use of paracetamol (Infulgan) to ensure sufficient duration of analgesia in the postoperative period in this category of patients.

Among the side effects (Table 2) caused by the use of pharmacological agents, dyspeptic disorders were observed in three patients of the study group and headache – in seven patients within the first three days after surgery. Dyspeptic disorders lasted during the first day and then disappeared without any therapy. Headaches may be associated primarily with bed exit after anesthesia and peculiarities of its performance. As a result of general therapeutic measures, rapid regression of these symptoms occurred.

After the use of opioid analgesics, such side effects as drowsiness (8 patients), nausea (5 patients), and headache (8 patients), probably caused both by the peculiarities of anesthesia and administration of opioids, were recorded in the comparison group. On the third day, one patient experienced urinary retention.

Therefore, administration of paracetamol (Infulgan) for perioperative analgesia during arthroscopic surgery in patients with intra-articular injuries of the knee joint and metal osteosynthesis for fractures of shin bones helps to reduce the intensity of pain in the postoperative period in order to avoid the need for opiate analgesia in patients with mild to moderate pain syndrome and prevent a number of side effects associated with the use of narcotic analgesics.

The data on the use of Infulgan in orthopedic patients with a moderate pain syndrome in terms of the dynamics of the pain intensity, duration of pain relief and time of anesthesia during the first 72 hours after surgery indicates its similar efficacy compared to Perfalgan (relevant parameters in the literature).

In case of using paracetamol at recommended doses and proper selection of patients, toxic effects of the drug have not been observed.

Introduction of parenteral paracetamol (Infulgan) at the Ukrainian pharmaceutical market allows to streamline perioperative multimodal analgesia to improve its safety and efficacy.