PARACETAMOL, AS A COMPONENT OF MULTIMODAL POSTOPERATIVE ANALGESIA IN SEVERE ORTHOPEDIC TRAUMA CARE

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Summary. The article is devoted to the optimization of multimodal postoperative analgesia in patients with severe orthopedic trauma. It has been proved that paracetamol, as a component of multimodal postoperative analgesia in patients with severe orthopedic trauma decreases the severity of pain syndrome and sedation effect, limits opioid analgesic consumption in postoperative period. Administration of the intravenous form of paracetamol — Infulgan — provides the stabilization of mean arterial pressure, heart rate, total peripheral resistance, and peripheral temperature. The elevated levels of hepatic transaminases in post-traumatic period were associated with severity of orthopedic trauma, but not with paracetamol prescription.

Key words: *severe trauma, multimodal analgesia, adverse events, paracetamol.*

INTRODUCTION

Today postoperative analgesia performed in the intensive care units is aimed, primarily, at prevention and management of pain syndrome in patients [1, 2]. The major components of the multimodal analgesia are as follows: neuraxial analgesia, non-steroidal anti-inflammatory drugs, narcotic analgesics, and inhibitors of cyclooxygenase (COX) [3, 4].

Paracetamol hardly can be called a non-steroidal anti-inflammatory drug as it provides rather weak anti-inflammatory effect, it is also a weak inhibitor of COX-1 and COX-2 so, it could not be numbered among non-steroidal anti-inflammatory drugs [5]. Unfortunately, such a mistake is rather common in some scientific articles and even in textbooks on pharmacology [6]. At the same time, paracetamol exhibits analgesic and antipyretic activities having no anti-inflammatory properties [7]. It is rather difficult to explain why it works like this. Paracetamol exhibits its antipyretic activities through inhibition of prostaglandin synthesis in the hypothalamus [7]. Analgesic effect of paracetamol can be explained by several hypotheses including COX-2 inhibition and impact on COX-3 in the central nervous system [6]. It should be emphasized that there are a lot of contradictory discussions concerning existence of COX-3. The other possible mechanism of action of paracetamol lies in its impact on the antinociceptive system through stimulation of descending serotoninergic fiber tract activity [6]. There is also an opinion suggesting action of paracetamol on peripheral opioid receptors [6].

According to the results of retrospective observational study conducted in Melbourne (Australia) in December 2009 – August 2010, paracetamol is more frequent prescribed to patients with sepsis, moreover, this medicine is prescribed regardless of the presence or absence of hyperthermia in a patient [8].

Paracetamol is absorbed in the small bowel, its bioavailability after oral administration amounts to 70 – 90 %; 5 – 10 % of paracetamol are protein bound that is why it has a rather large volume of distribution [7]. Being a unionized substance, paracetamol is liposoluble and penetrates through the blood-brain barrier [7]. Paracetamol is metabolized by the liver, 63 % bind with glucuronates and 34 % bind with sulphates that result in formation of water soluble metabolites [7]. Approximately 1 % of paracetamol is excreted unchanged in the urine. According to many authors, paracetamol overdose symptoms are observed after intake of 7.5 – 30 g or 15 mg/kg/day [7]. Basing on different literary sources, paracetamol in doses of 5-30 g is considered to be toxic [9].

Liver damage is conditioned by exhaustion of hepatic glutathione stocks, which leads to accumulation of n-acethylbenzoquinoneimine (NAPQI), one of the metabolites that causes liver damage. Moreover, after histopathological examination, liver damage looks like centrilobular necrosis [9]. Chronic liver failure due to regular administration of paracetamol occurs rather seldom [9].

Notwithstanding the extensive discussions on hepatotoxicity of paracetamol described in the medical literature, nephrotoxicity of this drug product often remains beyond the issue [10]. Renal failure due to paracetamol consumption occurs on prolonged administration of paracetamol during 2 – 5 days in doses significantly lower than hepatotoxic [10]. Renal damage occurs regardless of liver damage [10]. Paradoxically that prescription of glutathione as a main component of the detoxification therapy in paracetamol overdose may result in the formation of nephrotoxic glutathione compounds with following activation of caspases and lysosomal enzymes, which, in their turn, provoke apoptosis leading to the renal dysfunction [10]. Pathohistological examination of such patients reveals acute renal tubular necrosis [10].

Recommendations given in 2008 concerning usage of paracetamol as a component for postoperative analgesia run as follows: Paracetamol is recommended as an important component of multimodal analge-

sia either in mild pain syndrome (VAS < 4 points), moderate pain syndrome (VAS > 4 points, duration of pain syndrome is less than 3 days) and in severe pain syndrome (VAS > 6 points, duration of pain syndrome is more than 7 days) [11]. Paracetamol is recommended both for preemptive analgesia in a dose of 1 g i.v., and for postoperative analgesia [11]. Standard daily dose of paracetamol is 4 g per day; this dose is reduced to 2 – 3 g per day for patients with renal dysfunction [11]. The following criteria are taken into account in assessment of paracetamol effects: intensity of pain syndrome (VAS), sedation level, respiratory rate, and side effects [11].

Paracetamol is considered to be safe in pregnant, it does not cause spontaneous termination of pregnancy, and has no teratogenic effect [12].

A new form of paracetamol for intravenous infusion – Infulgan (Yuria Pharm, Ukraine) has appeared on the Ukrainian pharmaceutical market.

The aim of the study was to evaluate effects of Infulgan as a component of multimodal postoperative analgesia as well as its impact on severity of pain syndrome and incidence of adverse events in patients with severe orthopedic trauma.

STUDY OBJECT AND METHODS

42 patients aged 17 – 58 years old with prevailing pelvic ring trauma accompanied with severe concomitant injury were examined. Trauma severity in accordance with the ISS scale amounted to (25.6 ± 5.7) points. Severity of state of the surgical patients at admission date against the criteria of APACHE II amounted to (24.1 ± 5.9) points. Level of consciousness at admission date against the criteria of Glasgow Coma Scale amounted to (11.4 ± 3.6) points. The study included surgical patients who stayed in the intensive care unit for more than 3 days and demanded multimodal postoperative analgesia.

In both groups, the following curative measures were taken: infusion and transfusion therapy; anticoagulation reversal; continuous mechanical lung ventilation; adrenomimetic correction with norepiniphrine; early enteral feeding in the quantity of 35 kkal/kg; prophylaxis of stress ulceration with proton pump inhibitors in a dose of 40 mg/day; prophylaxis of deep venous thrombosis with low molecular weight heparins; de-escalation antibacterial therapy.

Multimodal postoperative analgesia in surgical patients was aimed at prevention and treatment of pain syndrome and it was assessed against criteria of VAS and integrative sedation scale as well as against values of mean blood pressure, heart rate, total peripheral resistance, cardiac output, doses of administered morphine, body temperature, activity of AlAT and AsAT, and international normalized ratio (INR). The data was evaluated in 6, 12, 24, 36, 48 and 72 hours of patient admission in the intensive care unit.

Postoperative multimodal analgesia in 21 patients of group 1 (control group) consisted of: ketorolac i.m. 30 mg every 8 hours, nefopam i.m. 20 mg every 6 hours, morphine i.m. 10 mg on demand if planned therapy was ineffective. In patients of group 2 (study group) the same complex of multimodal postoperative analgesia was supplemented with the planned intravenous infusion of paracetamol 1 g 4 times daily. Conduction of prolonged epidural analgesia in this category of patients was technically impossible as all patients had a severe pelvic ring trauma to be stabilized through adjustment of external fixation device.

Differences between study's stages were evaluated using repeated measures analysis of variance, and significance of differences of repeated measures was evaluated using Student's t-test with Bonferroni correction. Significance of differences between groups was evaluated using Student's t-test.

Table 1

Severity of pain syndrome in traumatized patients

Index	Time of p/o period, hour	Group 1	Group 2
VAS, points	6	4,5 ± 0,03	4,3 ± 0,04; p2=0,96
	12	4,0 ± 0,04; p1 =0,96	3,3 ± 0,03; p1=0,83; p2=0,24
	24	3,8 ± 0,03; p1 =0,91	3,0 ± 0,02; p1 =0,71 ; p2=0,15
	36	3,7 ± 0,02; p1 =0,82	2,7 ± 0,01; p1=0,54; p2=0,04
	48	3,6 ± 0,02; p1 =0,76	2,5 ± 0,02; p1 =0,25; p2=0,03
	72	3,3 ± 0,03; p1 =0,74	2,5 ± 0,02; p1 =0,15; p2=0,09
Level of sedation on the integrative scale, points	6	8,0 ± 0,07	8,3 ± 0,08; p2=0,96
	12	10,0 ± 0,12; p1 =0,65	13,3 ± 0,13; p1 =0,23; p2=0,14
	24	10,0 ± 0,28; p1 =0,65	14,0 ± 0,22; p1=0,15; p2=0,04
	36	11,0 ± 0,45; p1 =0,45	15,7 ± 0,31; p1 =0,09; p2=0,03
	48	13,1 ± 0,42; p1 =0,73	16,1 ± 0,32; p1=0,08; p2=0,09
	72	12 ± 0,33; p1 =0,21	15,5 ± 0,32; p1=0,09; p2=0,12
Doses of administered morphine, (total), mg	6	20,1 ± 0,87	10,3 ± 0,98; p2=0,04
	12	40,5 ± 1,12; p1 =0,05	20,3 ± 1,23; p1=0,05; p2=0,02
	24	60,2 ± 1,28; p1=0,03	24,0 ± 1,32; p1 =0,03; p2<0,01
	36	91,6 ± 2,45; p1 =0,01	35,7 ± 3,36; p1<0,01 ; p2<0,01
	48	113,1 ± 3,32; p1 <0,01	56,1 ± 2,32; p1<0,01 ; p2<0,01
	72	152 ± 4,33; p1<0,01	75,5 ± 3,32; p1<0,01; p2<0,01

Notes: p1 – significance of differences in comparison with the first stage of the study;
p2 – significance of differences in comparison with the control group.

RESULTS AND DISCUSSIONS

According to the study results represented in Table 1, paracetamol turned out to be a very effective agent in respect of limitation of postoperative pain syndrome intensity in patients with severe orthopedic trauma.

Thus, intensity of pain syndrome on VAS in patients from the paracetamol group was 32 % lower by third day of the study. Moreover, patients from this group were more active (15 points versus 12 points on the integrative sedation scale), and total dose of morphine administered for pain relief in the study group was two times less than in the control group. This fact is particularly important as administration of narcotic analgesics in postoperative period often associates with development of respiratory depression, prolongation of timing of extubation, occurrence of nausea and vomiting, gastrointestinal motility disorder. Our results conform with the data obtained by A. Choundchuri (2011). This study demonstrated that administration of paracetamol as a component of preemptive analgesia during laparoscopic cholecystectomy surgery resulted in limitation of pain syndrome intensity in postoperative period (3.3 versus 5.2 on VAS), as well as allowed to reduce quantity of fentanyl administered during the first 24 hours of postoperative period (50 mg versus 150 mg) [13]. The study conducted by D. Memis and M. T. Inal (2010) also demonstrated that routine administration of paracetamol in a dose of 4 g/day after major surgeries significantly limited severity of pain syndrome, reduced administration of narcotic analgesics in postoperative period as well as reduced timing of extubation and incidence of nausea and vomiting in postoperative period [14]. However, certain authors (A.D. Samson, N.G. Hunfeld, 2010), having evaluated such pharmacokinetic parameters as half-life, volume of distribution, paracetamol clearance when administered in a dose of 1 g 4 times per day to patients in critical condition, concluded that such a dose is insufficient for reaching proper analgesic effect [15]. Primarily, it is attributable to low concentration of paracetamol in blood plasma when administered in the recommended dose [15]. That is why efforts of pharmacologists and clinicians are to be directed to the development of a new administration scheme of paracetamol aimed at safer and more adequate analgesia in critically ill patients [15]. The second, not least important, aspect to our opinion is impact of paracetamol on hemodynamics indices in patients with severe trauma. According to Table 2, in the group where paracetamol was administered as a component of multimodal postoperative analgesia, levels of mean blood pressure and total peripheral resistance were higher while tachycardia intensity was lower than in the control group.

Table 2

Indices of hemodynamics and peripheral temperature in traumatized patients

Index	Time of p/o period, hour	Group 1	Group 2
Mean blood pressure, mm Hg	6	74,5 ± 1,73	76,3 ± 2,4; p2=0,98
	12	72,4 ± 2,04; p1 =0,91	83,3 ± 1,53; p1 =0,73; p2=0,42
	24	76,8 ± 3,03; p1 =0,99	85,4 ± 0,02; p1 =0,71; p2=0,35
	36	73,7 ± 2,62; p1=0,82	88,7 ± 1,91; p1=0,66; p2=0,24
	48	74,6 ± 2,02; p1 =0,99	90,5 ± 2,95; p1=0,55; p2=0,15
	72	73,3 ± 2,14; p1 =0,81	94,5 ± 3,32; p1 =0,45; p2=0,09
Heart rate, bpm	6	121,1 ± 4,47	119,2 ± 4,48; p1 =0,91; p2=0,92
	12	105,1 ± 3,56; p1 =0,81	104,2 ± 3,98; p1 =0,81; p2=0,94
	24	98,2 ± 0,65; p1=0,65	90,3 ± 3,56; p1 =0,71; p2=0,84
	36	101,2 ± 3,25; p1 =0,75	91,3 ± 4,32; p1 =0,72; p2=0,71
	48	103,4 ± 3,45; p1=0,79	84,5 ± 4,68; p1 =0,65; p2=0,62
	72	95,5 ± 3,23; p1=0,77	85,6 ± 3,23; p1=0,66; p2=0,61
Total peripheral resistance, dyne x sec/sm^5	6	1314 ± 12,87	1320 ± 14,28; p2=0,93
	12	1212 ± 11,42; p1 =0,81	1230 ± 11,24; p1 =0,82; p2=0,97
	24	1140 ± 15,82; p1=0,73	1210 ± 11,23; p1=0,79; p2=0,84
	36	1060 ± 10,25; p1 =0,68	1224 ± 12,34; p1 =0,81; p2=0,70
	48	960 ± 13,34; p1 =0,41	1221 ± 12,88; p1=0,82; p2=0,35
	72	984 ± 9,33; p1=0,32	1234 ± 13,82; p1=0,93; p2=0,21
Peripheral temperature, degrees Celsius	6	36,0 ± 0,25	36,1 ± 0,06; p2=0,98
	12	36,5 ± 0,12; p1 =0,85	36,6 ± 0,03; p1 =0,85; p2=0,95
	24	36,9 ± 0,08; p1 =0,73	36,8 ± 0,04; p1=0,73; p2=0,91
	36	37,1 ± 0,08; p1 =0,65	36,9 ± 0,09; p1 =0,72; p2=0,93
	48	37,5 ± 0,06; p1 =0,54	37,1 ± 0,04; p1 =0,71; p2=0,72
	72	38,1 ± 0,07; p1 =0,43	37,3 ± 0,03; p1=0,53; p2=0,70

Notes: p1 – significance of differences in comparison with the first stage of the study;
p2 – significance of differences in comparison with the control group.

This is, probably, attributable to the lower doses of morphine administered in the study group and limitation of its vasodilatory effect comparing to the control group. Usage of paracetamol did not cause development of hypothermia in patients and moreover, administration of this medicine limited intensity of systemic inflammatory response syndrome by the third day post trauma. Notwithstanding that certain investigators (M. Boyle, 1997; M. Hersch 2004; A. Krajcova, 2012) describe development of hypotension, reduced cardiac output and total peripheral resistance in the critically ill patients after intravenous paracetamol infusion, it could be attributed to hyperthermia management after administration of paracetamol to the patients at the background of systemic inflammatory response syndrome [16 18].

And finally, one more important aspect: whether paracetamol in a dose of 4 g/day affect liver function. It is of extreme importance, considering that a severe orthopedic trauma almost always leads to development of coagulopathy and often demands packed red cell and plasma transfusion.

According to the study data represented in Table 3, within 3 days of post-traumatic period, there were registered elevated levels of transaminases along with normalization of international normalized ratio by the twelfth hour of observation in both groups.

Table 3

Indices of liver function in traumatized patients

Index	Time of p/o period, hour	Group 1	Group 2
AlAT, U	6	1,45 ± 0,03	1,51 ± 0,03; p2=0,98
	12	1,34 ± 0,01; p1 =0,85	1,41 ± 0,02; p1 =0,81; p2=0,83
	24	1,13 ± 0,02; p1 =0,70	1,12 ± 0,04; p1 =0,65; p2=0,91
	36	0,94 ± 0,03; p1 =0,65	0,85 ± 0,05; p1 =0,71; p2=0,81
	48	0,86 ± 0,04; p1 =0,51	0,81 ± 0,03; p1=0,65; p2=0,85
	72	0,74 ± 0,02; p1=0,42	0,76 ± 0,02; p1=0,55; p2=0,89
AsAT, U	6	1,53 ± 0,05	1,52 ± 0,06; p2=0,94
	12	1,56 ± 0,04; p1 =0,94	1,44 ± 0,04; p1 =0,81; p2=0,83
	24	1,54 ± 0,03; p1 =0,99	1,43 ± 0,07; p1 =0,82; p2=0,81
	36	1,38 ± 0,02; p1 =0,78	1,18 ± 0,04; p1=0,54; p2=0,66
	48	1,21 ± 0,03; p1 =0,73	1,15 ± 0,03; p1 =0,52; p2=0,76
	72	1,05 ± 0,06; p1 =0,55	0,94 ± 0,08; p1 =0,38; p2=0,72
International normalized ration	6	1,70 ± 0,12	1,6 ± 0,04; p2=0,97
	12	1,10 ± 0,17; p1 =0,51	1,05 ± 0,05; p1=0,52; p2=0,95
	24	1,0 ± 0,13; p1 =0,53	1,02 ± 0,03; p1 =0,51; p2=0,96
	36	0,98 ± 0,09; p1=0,48	1,01 ± 0,05; p1 =0,48; p2=0,88
	48	0,96 ± 0,08; p1 =0,45	0,98 ± 0,04; p1 =0,46; p2=0,95
	72	0,91 ± 0,08; p1 =0,31	0,99 ± 0,03; p1=0,47; p2=0,71

Notes: p1 – significance of differences in comparison with the first stage of the study;
p2 – significance of differences in comparison with the control group.

It is attributable to the fact that liver is a central regulator of systemic inflammatory response that occurs due to severe traumatic injury [19]. Liver function abnormality immediately after trauma is attributed to the developing liver edema. It was demonstrated in animal model that liver weight and ratio of liver weight to body weight extremely increased by the 2nd - 7th day post trauma [20]. Taking into account that protein content in the liver is reduced, it is suggested that liver weight increase is attributed to edematization rather than to the increase in the amount of hepatocytes or enhancement in protein production. Liver edema leads to hepatocellular damage and release of liver enzymes [21]. Thus, in post-traumatic period, serum levels of alkaline phosphatase, glutamyl oxalate transaminase and glutamine-pyruvate transaminase are significantly increased. AlAT and AsAT levels as well as level of alkaline phosphatase increased by 50 - 200 % in comparison with normal values [22]. At the first week post trauma, there were registered maximum levels of the above mentioned enzymes, and normalization of these indices was recorded at the third - fifth week post trauma [22]. It should be emphasized that we have not revealed significant differences between groups concerning both transaminase levels, and international normalized ratio level.

CONCLUSIONS

1. Usage of paracetamol, as a component of multimodal postoperative analgesia in patients with severe orthopedic trauma decreases the severity of pain syndrome and sedation effect, reduces opioid analgesic consumption in postoperative period.
2. Administration of the intravenous form of paracetamol — Infulgan — provided stabilization of mean arterial pressure, heart rate, total peripheral resistance, and peripheral temperature.
3. The elevated levels of hepatic transaminases in post-traumatic period were associated with severity and extensiveness of orthopedic trauma, but not with paracetamol prescription.

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