Dmytriiev Dmytro, Nazarchuk Oleksandr. Pre-emptive administration of intravenous acetaminophen with transversus abdominis plane block (tap-blocke) in the prevention of fentanil-induced hyperalgesia in pediatric oncological patient undergoing abdominal surgery. Journal of Education, Health and Sport. 2015;5(10):98-107. ISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.32514
http://ojs.ukw.edu.pl/index.php/johs/article/view/2015%3B5%2810%29%3A98-107
https://pbn.nauka.gov.pl/works/659929
Formerly Journal of Health Sciences. ISSN 1429-9623 / 2300-665X. Archives 2011–2014 http://journal.rsw.edu.pl/index.php/JHS/issue/archive

Deklaracja.
Specyfika i zawartość merytoryczna czasopisma nie ulega zmianie.
Zgodnie z informacją MNiSW z dnia 2 czerwca 2014 r., że w roku 2014 nie będzie przeprowadzana ocena czasopism naukowych; czasopismo o zmienionym tytule otrzymuje tyle samo punktów co na wykazie czasopism naukowych z dnia 31 grudnia 2014 r.
The journal has had 5 points in Ministry of Science and Higher Education of Poland parametric evaluation. Part B item 1089. (31.12.2014).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 05.08.2015. Revised 05.09.2015. Accepted: 20.10.2015.

UDC: 616-089.5-053.2: 616-006

PRE-EMPTIVE ADMINISTRATION OF INTRAVENOUS ACETAMINOPHEN WITH TRANSVERSUS ABDOMINIS PLANE BLOCK (TAP-BLOCKE) IN THE PREVENTION OF FENTANIL-INDUCED HYPERALGESIA IN PEDIATRIC ONCOLOGICAL PATIENT UNDERGOING ABDOMINAL SURGERY

Dmytro Dmytriiev, Oleksandr Nazarchuk

Department of Anesthesiology and Intensive care,
Vinnytsya National Pirogov Memorial Medical University

Abstract

Background: Acetaminophen is a selective COX-2 agonist that has been shown to decrease the intensity of opioid-induced hyperalgesia (OIH) in children. We aimed to investigate the effects of preemptive administration of intravenous acitomenofen in the prevention of high-dose **fentanil**-induced hyperalgesia in pediatric patients.

Methods: 45 patients of American Society of Anesthesiologists physical status 1-3 undergoing abdominal surgery were randomly assigned to one of the following three groups. each of which received either IV acetaminophen (an initial dose of 1.5 ml/kg for 40 min before before the induction of anesthesia) or placebo saline 40 min before the induction of anesthesia and intraoperative fentanil infusion: group LFH received a placebo and 0.05 μg/kg/min fentanil; group FH received a placebo and 0.3 μg/kg/min fentanil; and group AFH received IV preemptive administration acetaminophen and TAP-blocke bupivacaine 0,3 mg/kg.

Results: The mechanical hyperalgesia threshold 12 hr after surgery was significantly lower in group FH than in the other two groups. Postoperative pain intensity using visual analog scale (VAS) and cumulative volume of a patient controlled analgesia (PCA) containing morphine over 12 hr were significantly greater in group FH than in group AFH. The time to the

first postoperative analgesic requirement was significantly shorter in group RH than in the other two groups. The sevoflurane requirement was significantly greater in group LFH than in the other groups. The frequency of hypotension and bradycardia was significantly higher, but shivering and postoperative nausea and vomiting were significantly lower in group AFH than in the other two groups.

Conclusions: High-doses of fentanil induced hyperalgesia, which presented a decreased mechanical hyperalgesia threshold, enhanced pain intensity, a shorter time to first postoperative analgesic requirement, and greater morphine consumption, but IV preemptive administration acetaminophen alleviated those symptoms. IV preemptive administration acetaminophen may be an effective treatment option for preventing or attenuating OIH.

Key words: IV preemptive administration acetaminophen, Opioid-induced hyperalgesia, fentanil, TAP-blocke.

Introduction. During tissue injury, prostaglandin-E2 (PGE2) is produced by the activation of the enzyme cyclooxygenase (COX) to play an important role in inflammatory hyperalgesia. PGE2 sensitizes peripheral nociceptors through the activation of PGE2 receptors (EP) [1]. This sensitization, characterized by a reduction of nociceptive threshold and by an increase in peripheral afferent neuron responsiveness, is the main feature of inflammatory hyperalgesia in the peripheral tissue. The widespread use of nonsteroidal anti-inflammatory drugs to control inflammatory hyperalgesia exemplifies the relevance of PGE2 for the development of inflammatory hyperalgesia. These drugs decrease peripheral inflammatory hyperalgesia by inhibiting COX and, therefore, by preventing the synthesis of PGE2 [2].

Although acetaminophen potently reduces pain and fever, its mechanism of action has so far not been satisfactorily explained. It inhibits both COX-1 and COX-2 weakly in vitro, but reduces prostaglandin synthesis markedly in vivo. In mouse macrophage J774.2 cells, COX-2 induced for 48 hr with high concentrations of NSAIDs is more sensitive to inhibition with paracetamol than endotoxin-induced COX-2. In the rat pleurisy model of inflammation, a second peak of COX-2 protein appears 48 hr after administration of the inflammatory stimulus, during the resolution phase of the inflammatory process. Inhibition of the activity of this late-appearing COX-2 with indomethacin or a selective COX-2 inhibitor, delays resolution and the

inflammation is prolonged. Cultured lung fibroblasts also express COX-2 activity after stimulation with IL-1beta which is highly sensitive to inhibition with acetaminophen. Thus, evidence is accumulating for the existence of a COX-2 variant or a new COX enzyme which can be inhibited with acetaminophen [3].

Fentanil is an ultra-short-acting μ-opioid receptor agonist associated with a predictable and rapid recovery that is independent of the dose and duration of infusion. Its unique pharmacokinetic characteristics make it an effective anesthetic adjuvant, commonly used in general anesthesia [4]. However, considerable evidence suggests that exposure to high-dose remifentanil paradoxically enhances pain sensitivity and increases analgesic requirements [5-7].

In this study, we evaluated the antihyperalgesia effects of a intravenous administration of acetaminophen on highdose fentanil-induced hyperalgesia, which presented a decreased mechanical hyperalgesia threshold in pediatric patients, enhanced pain intensity, a shorter time to first postoperative analgesic requirement, and greater morphine consumption.

Materials and methods. We obtained approval from Ethics Committee of our institute and written informed consent from all participants. 45 patients (n = 15 per group) American Society of Anesthesiologists physical status 1-3 patients aged 10-15 (12,4 ± 1,5) years who were scheduled for colorectal surgery due to oncological issues were enrolled in the study.

Exclusion criteria included (1) allergy to acetaminophen, (2) clinically significant medical or psychiatric conditions, (3) patients currently on opioid-containing medications, (4) immediate extubation was not planned after surgery (5) they were unable to self administer opioids.

On the day before surgery, during the preoperative anaesthtic evaluation, patients were taught how to use the visual analog scale (VAS) and the patient-controlled analgesia (PCA) device. They were instructed to self-deliver analgesia whenever they began to feel pain. Intraoperatively patients were monitored using pulse oximeter, automated blood pressure (BP) cuff, electrocardiogram (ECG), and end-tidal CO2 (ETCO2) devices. In addition, arterial and urinary catheters were inserted as part of the patient's management.

The patients were randomly assigned using a computer generated random number table into one of three treatment groups, each of which received either acetaminophen (IV infusion; an initial dose of 1.5 ml/kg for 15 min before the induction of anesthesia) or placebo saline 15 min before the induction of anesthesia and intraoperative fentanil infusion: group LFH received a placebo and 0.05 μg/ kg/min fentanil; group FH received a placebo and 0.3 μg/kg/ min fentanil; and group AFH received acetaminophen and TAP-blocke bupivacaine 0,3 mg/kg. Induction of anesthesia was commenced with a slow (30-60 s) intravenous (i.v.) bolus dose of fentanil (1

μg/kg), followed by propofol (2 mg/kg); tracheal intubation was facilitated with rocuronium (0.9 mg/kg) in all groups.

As mentioned above, infusion of acitomenofen or fentanil in all groups was fixed, and anesthesia was maintained with sevoflurane and an oxygen/air mixture (fraction of oxygen, 40%). When sevoflurane was required, its administration was started at the end-tidal concentration of 1 minimum alveolar concentration (MAC), and the concentration was adjusted by a 1% stepwise titration according to acceptable hemodynamic limits (mean arterial blood pressure between -30% and +15% and heart rate between -40% and +15%) and to a target bispectral index (BIS) between 40 and 60. Atropine (0.2 mg) administered if a patient's preoperative baseline values went below the acceptable limits. When BIS values reached 80 and spontaneous breathing was achieved, extubation was performed.

Each patient was administered analgesics using a PCA pump containing morphine (60 mg) in a total volume of 100 ml of saline. This device was set to deliver a basal infusion of 2 ml/hr and bolus doses of 0.5 ml with a 15 min lockout period. Postoperative pain intensity was documented using a 100 mm linear VAS. The VAS consisted of a straight line with the left end of the line representing no pain and the right end of the line representing the worst pain. Patients were asked to mark the position on the line corresponding to their perception of pain. An i.v. dose of acetaminophen (1,5 ml/kg) was administered if patients reported a VAS score ≥ 40.

The mechanical hyperalgesia threshold was measured preoperatively and 12 hr after surgery using Von Frey filaments (*BiosebTM, Chaville, France*) on peri-incisional areas, 2 cm above from the perpendicular line of the optical port site. This device consists of 20 monofilaments of constant length with a stepwise progression of diameters. The numerical grade of the filaments (1.65-6.65) corresponds to a logarithmic function of the equivalent forces of 0.008-300 g.

When the tip of a fiber of given length and diameter is pressed against a test area at a right angle, the applied force increases as the researcher continues to advance the probe, until the fiber bends. After the fiber bends, further advancement of the probe may induce more bending, but does not apply more force to the test area. This makes it possible to apply reproducible forces within a wide tolerance range to the tested surface. The force is continuously applied for 1 s and then removed. Subjects are instructed to respond "yes" to indicate that contact was felt during the stimulation or "no" to indicate that contact was not felt during the stimulation. If the subject reports a negative answer, a filament with a larger diameter is used and applied with increasing intensity until the subject reacts. The mechanical hyperalgesia threshold was defined as the lowest force (g/mm2) necessary to bend a Von Frey filament, which was perceived to be painful. The primary endpoint was a mechanical hyperalgesia threshold at 12 hr after surgery.

Secondary endpoints were the time to the first postoperative analgesic requirement, postoperative pain intensity using VAS, and cumulative volume of a PCA containing morphine over 24 hr. Side effects related to the study drugs included hypotension, bradycardia, dysrhythmia, shivering, and postoperative nausea and vomiting (PONV). Shivering was treated using a forced-air warming blanket. Nausea or vomiting was treated with i.v. ondansetron (4 mg). A preliminary investigation showed that the means of the three treatment groups (group LFH, group FH, and group AFH) for mechanical hyperalgesia threshold after surgery were 132, 84, and 116 g/mm2, respectively, with effect size of 0.37 and a standard deviation among subjects of 39.55 g/mm2. Thus, a sample size of 15 patients per group was needed to demonstrate a significant difference with a power of 80% and an α-coefficient of 0.05.

Assuming a 10% dropout rate, the final sample size was determined to be 15 patients per group. The results are presented as mean ± SD or number (percentage) of patients. Comparisons of age, body weight, % volume of sevoflurane, duration of anesthesia, mechanical hyperalgesia threshold, time to first postoperative analgesic requirement, pain intensity, and cumulative PCA volume over 24 hr after surgery among the groups were conducted using one-way ANOVA.

Post-hoc comparisons were performed with Bonferroni correction of the significance level. Chi-square tests were used to analyze categorical data, such as hypotension, bradycardia, shivering, dysrhythmia, and PONV. $P < 0.05$ was considered statistically significant.

Results. A total of 45 patients were assessed for eligibility and received study medication after randomization. There were no significant differences between the three groups with respect to age, weight, duration of anesthesia, or perioperative tympanic temperature. Extubation time after surgery was significantly longer in group LFH than in the other two groups. The % volume of desflurane was significantly higher in group LFH than in the other two groups, and that in group AFH was significantly lower than in group FH.

The time to first postoperative analgesic requirement was significantly shorter in group LFH than in the other two groups. Analgesic consumption (morphine) during PACU stay was significantly higher in group LFH than in the other two groups. Pain intensity using VAS was significantly greater in group FH than in group AFH and group LFH at 24 hr and 12 hr after surgery, respectively. The preoperative mechanical hyperalgesia threshold was not significantly different between the three groups (Table 1).

Table 1

Demographic and Anesthetic Data

Indexes	Group LFH (n = 15)	Group FH (n = 15)	Group AFH (n = 15)
Age (yr)	12,6±1,6	12,4±1,2	12,8±1,6
Weight (kg)	37,2±4,4	36,8±4,8	38,0±5,1
Gender: male/female	8/7	7/8	6/9
Duration of anesthesia (min)	133,8±12,4	137,4±14,0	136,2±13,2
Extubation time after surgery (min)	10,6±2,2*	7,4±2,0	7,8±1,9
Infusion of fluid (ml)	674,8±60,2	680,4±64,4	678,2±63,8
Mean volume of sevoflurane (%)	7,3±0,4*	4,8±0,5†	3,4±0,4

Values are expressed as mean ± SD. Group LFH: placebo and 0.05 μg/kg/min fentanil, group FH: placebo and 0.3 μg/kg/min fentanil, and group AFH: acetaminophen and TAP-blocke bupivacaine 0,3 mg/kg. *P < 0.05 versus the other 2 groups. †P < 0.05 versus group AFH

The mechanical hyperalgesia threshold around the surgical incision 24 hr after surgery was significantly lower in group FH than in the other two groups. The volume of PCA containing morphine was significantly greater in group FH than in the other two groups (Table 2).

Table 2

Clinically Relevant Pain and Mechanical Hyperalgesia Threshold

Indexes	Group LFH (n = 15)	Group FH (n = 15)	Group AFH (n = 15)
Time to first postoperative analgesic requirement (min)	38,8±6,0	24,4±4,2*	39,0±6,1
Analgesic consumption (acetaminophen) during their PACU stay (mg)	522,8±22,4	602,4±20,4*	508,4±18,4
Pain intensity VAS 24 hr after surgery	22,4±2,4	26,0±3,2†	17,2±2,2
Preoperative mechanical hyperalgesia threshold (g/mm2)	196,2±32,4	195,8±34,2	196,0±33,8
Mechanical hyperalgesia threshold at 24 hr after surgery (g/mm2)	130,4±30,4	84,8±29,2†	132,4±28,2
Cumulative PCA volume containing morphine (ml) for 24 hr after surgery	4,4±0,9	6,2±0,8*	4,6±0,7

Values are expressed as mean ± SD. PACU: postanesthesia care unit. Group LFH: placebo and 0.05 μg/kg/min fentanil, group FH: placebo and 0.3 μg/kg/min fentanil, and group AFH: acetaminophen and TAP-blocke bupivacaine 0,3 mg/kg. *P < 0.05 versus the other 2 groups. †P < 0.05 versus group AFH

The frequency of hypotension and bradycardia was significantly higher in group AFH than in the other two groups. Postanesthetic shivering was significantly lower in group AFH than in the other two groups, and that in group FH was significantly higher than in group LFH. PONV was significantly lower in group AFH than in the other two groups, and that in group LFH was significantly higher than in group FH (Table 3).

Table 3

Postoperative Side Effects Group

Indexes	Group LFH (n = 15)	Group FH (n = 15)	Group AFH (n = 15)
Hypotension	1 (6.6)	2 (13.3)	2 (13.3)
Bradycardia	1 (6.6)	1 (6.6)	1 (6.6)
Dysrhythmia	1 (6.6)	1 (6.6)	0 (0)
Shivering	3 (20)	4 (26.6)	1(6.6)*
PONV	8 (53.3)	10 (66.6)	2 (13.3)*

Values are expressed as numbers (%). PONV: postoperative nausea and vomiting. Group LFH: placebo and 0.05 μg/kg/min fentanil, group FH: placebo and 0.3 μg/kg/min fentanil, and group AFH: acetaminophen and TAP-blocke bupivacaine 0,3 mg/kg. *P < 0.05 versus group the other 2 groups. †P < 0.05 versus group AFH.

Discussion. The major finding of this study was that IV preemptive administration acetaminophen (an initial dose of 1.5 ml/kg for 40 min before before the induction of anesthesia) attenuated high-dose fentanil-induced hyperalgesia in pediatric patients undergoing OAS. OIH is characterized by a paradoxical increase in pain intensity, distribution, or sensitivity in patients receiving highdoses or long durations of opioids for the treatment of pain [5]. As a result, patients become more sensitive to certain painful stimuli. However, epidemiologic reports regarding the incidence or prevalence of OIH are limited.

Although the precise molecular mechanism of OIH is not yet understood, acute receptor desensitization via uncoupling of the receptor from G-proteins, up-regulation of the cAMP pathway, activation of the N-methyl-D-aspartate (NMDA)-receptor system, and descending facilitation have been proposed to be involved. Of these, the central NMDA system is considered the most likely player. NMDA receptors are comprised of two types of subunits: the principal subunit NR1 and the modulatory subunit NR2A-D. Particularly crucial is the NMDA receptor 2B (NR2B) subunit, which plays an important role in spinal dorsal horn sensory pathways [10,11].

In the present study, we found that intraoperative high-dose fentanil induced a decreased mechanical hyperalgesia threshold, enhanced pain intensity, shorter time to first post operative analgesic requirement, and greater morphine con sumption, all indicative of OIH. Enhanced tyrosine phosphorylation of NR2B in the spinal cord is associated with fentanil-induced postoperative hyperalgesia. In fact, it plays a key role in the NMDA receptor activation, and contributes to nociceptor activity-induced spinal plasticity and the development of central sensitization that leads to OIH [11].

Strategies for preventing, reversing, or managing OIH have been attempted. These include the NMDA receptor antagonists ketamine [11] or magnesium [7], the GABA receptor antagonist propofol [1,8], the α2 agonists clonidine [1] or dexmedetomidine [2,3,5], the β-blocker propranolol [12], and the COX-2 inhibitor parecoxib [14]. Acetaminophen, a selective and potent COX-2 and COX-3 receptor agonist attenuates hig acetaminophen h-dose fentanil-induced hyperalgesia by decreasing spinal tyrosine phosphory lation of the NR2B subunit [10].

As mentioned above, in the present study, the IV preemptive administration acetaminophen (group AFH) alleviated clinically relevant pain by relieving symptoms such as enhanced pain intensity, inducing a shorter time to first post operative analgesic requirement and high morphine consumption; mechanically evoked pain up to 12-24 hr after surgery was also alleviated. It has been shown that the effect of IV preemptive administration acetaminophen on the cumulative consumption of morphine persisted for 24 hr, and its effect on postoperative pain intensity for 48 hr, as compared to controls [14].

In the present study, the acetaminophen (group AFH) significantly reduced the sevoflurane requirement for anesthetic maintenance by 37%, and 13% compared with the groups receiving placebo concomitant with low- or high-dose fentanil (groups LFH and FH, respectively). In the present study, we found that the frequency of hypotension and bradycardia in group AFH was significantly higher, and PONV was significantly lower, as compared to the other two groups. However, acetaminophen combined with high-doses of fentanil should be used cautiously, as this present study showed that patient's preoperative hemodynamic baseline values in group ARH significantly went below the acceptable limits compared to the two groups. Postanesthetic shivering or OIH is associated with highdose fentanil and may be prevented by NMDA receptor antagonists [15]. In the present study, we found that OIH and shivering induced by high-dose fentanil were alleviated by acetaminophen. The findings of the present study provide an indirect support to the fact that antihyperalgesic and antishivering effects of α2 adrenergic receptor agonists are associated with NMDA receptors.

Conclusion

High-doses of fentanil-induced hyperalgesia, which present a decreased mechanical hyperalgesia threshold, enhanced pain intensity, shorter time to first postoperative analgesic requirement, and greater morphine consumption. Acetaminophen preemptive infusion efficiently alleviate OIH symptoms. Therefore, acetaminophen preemptive infusion may be a novel and effective treatment option for preventing or attenuating OIH. Further studies are required to investigate the use of acetaminophen preemptive analgesia as part of a multimodal approach for OIH.

References

1. Omote K, et al. Effects of a novel selective agonist for prostaglandin receptor subtype EP4 on hyperalgesia and inflammation in monoarthritic model. Anesthesiology. 2002;97(1):170–176.

2. Araldi D1, Ferrari LF, Lotufo CM, Vieira AS, Athié MC, Figueiredo JG, Duarte DB, Tambeli CH, Ferreira SH, Parada CA. Peripheral inflammatory hyperalgesia depends on the COX increase in the dorsal root ganglion. Proc Natl Acad Sci U S A. 2013;110(9):3603-8.

3. Botting R. Paracetamol-inhibitable COX-2.J Physiol Pharmacol. 2000 Dec;51(4 Pt 1):609-18.

4. Bürkle H, Dunbar S, Van Aken H. Remifentanil: a novel, shortacting, mu-opioid. Anesth Analg 1996; 83: 646-51.

5. Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. Clin J Pain 2008; 24: 479-96.

6. Singler B, Tröster A, Manering N, Schüttler J, Koppert W. Modulation of remifentanil-induced postinfusion hyperalgesia by propofol. Anesth Analg 2007; 104: 1397-403.

7. Lee C, Song YK, Jeong HM, Park SN. The effects of magnesium sulfate infiltration on perioperative opioid consumption and opioid-induced hyperalgesia in patients undergoing robot-assisted laparoscopic prostatectomy with remifentanil-based anesthesia. Korean J Anesthesiol 2011; 61: 244-50.

8. Virtanen R, Savola JM, Saano V, Nyman L. Characterization of the selectivity, specificity and potency of medetomidine as an alpha 2-adrenoceptor agonist. Eur J Pharmacol 1988; 150: 9-14.

9. Belgrade M, Hall S. Dexmedetomidine infusion for the management of opioid-induced hyperalgesia. Pain Med 2010; 11: 1819-26.

10. Koppert W, Sittl R, Scheuber K, Alsheimer M, Schmelz M, Schuttler J. Differential modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by S-ketamine and clonidine in humans. Anesthesiology 2003; 99: 152-9.

11. Gu X, Wu X, Liu Y, Cui S, Ma Z. Tyrosine phosphorylation of the N-Methyl-D-Aspartate receptor 2B subunit in spinal cord contributes to remifentanil-induced postoperative hyperalgesia: the preventive effect of ketamine. Mol Pain 2009; 5: 76.

12. Chu LF, Cun T, Ngai LK, Kim JE, Zamora AK, Young CA, et al. Modulation of remifentanil-induced postinfusion hyperalgesia by the β-blocker propranolol in humans. Pain 2012; 153: 974-81.

13. Tröster A, Sittl R, Singler B, Schmelz M, Schüttler J, Koppert W. Modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by parecoxib in humans. Anesthesiology 2006; 105: 1016-23.

14. Blaudszun G, Lysakowski C, Elia N, Tramèr MR. Effect of perioperative systemic α2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. Anesthesiology 2012; 116: 1312-22.

15. Komatsu R, Turan AM, Orhan-Sungur M, McGuire J, Radke OC, Apfel CC. Remifentanil for general anaesthesia: a systematic review. Anaesthesia 2007; 62: 1266-80.