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IMPACT OF REMIFENTANIL APPLICATION MODALITY ON POSTOPERATIVE PAIN AFTER BREAST CONSERVING SURGERY

Ana Cvetković, MD
Specialist of anesthesiology and reanimatology,
Institute for Oncology and Radiology of Serbia,
Belgrade, Serbia.
anadjurdjic@yahoo.com

Vera VojinovićGolubović, MD
Specialist of anesthesiology and reanimatology,
Institute for Oncology and Radiology of Serbia,
Belgrade, Serbia.

LjMitrovićJaćimović, MD
Specialist of anesthesiology and reanimatology,
Institute for Oncology and Radiology of Serbia,
Belgrade, Serbia.

D Miler Mirčić, MD
Institute for Oncology and Radiology of Serbia,
Belgrade, Serbia.

Abstract
Continual remifentanil use in anesthesia is related with postoperative hyperalgesia and opioid tolerance. Study investigates whether lowering remifentanil dose at the end of surgery impacts on pain decrease and need for rescue analgesics in postoperative period.

Keywords: Remifentanil, postoperative pain, opioid induced hyperalgesia, opioid tolerance.

1. INTRODUCTION
Remifentanil, selective μ –opioid agonist is commonly used during general anesthesia to reduce requirement of anesthetics and to reduce response to noxious stimuli[1]. Because of its pharmacodynamic and pharmacokinetic effects, remifentanil has been used in clinical anesthesia as an induction and maintenance agent and for postoperative pain management in the intensive care units. Even though remifentanil increases analgesia and respiratory depression in a dose-dependent manner, these effects disappear rapidly after discontinuing administration of the drug because of the extremely short elimination half-life[2-7]. These advantages of continual remifentanil use in anesthesia are followed with their disadvantages like paradoxical and pathological pain called opioide induced hyperalgesia (OIH) and opioid tolerance (OT)[8-9]. Tolerance can be overcome by increasing dose of the drug.OIH is a paradoxical response to an opioid, whereby a patient receiving opioid for the treatment of pain might actually have an increase in pain perception. Mechanisms of postoperative OIH and OT are still unclear. There are different assumptions. Central sensitization by activation of the N-methyl- D-aspartate (NMDA) receptors is probably responsible for opioid induced hyperalgesia[10,11]. Excitatory amino acids such as glutamate, aspartate, and substance P are released from excitatory synapse membranes through central sensitization and then activate postsynaptic NMDA receptors[12]. NMDA receptor blockers prevent central sensitization by inhibiting activation of excitatory amino

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acids such as glutamate on NMDA receptors. Ketamine[13,14,15,16] is a non-competitive and magnesium is a physiologic NMDA receptor blocker[17]. Several methods have been investigated to prevent opioid induced hyperalgesia. There are suggestions that stepwise tapering of high-dose remifentanil at the end of surgery could prevent long-term potentiation at synapses of the pain pathways and thus diminish postoperative pain and rescue analgesics during postoperative period[18]. This study investigates whether lowering remifentanil dose at the end of surgery impact on pain decrease, need for rescue analgesics and nausea appearance in postoperative period.

2. METHODS

This retrospective randomised study includes 25 female patients, ASA 2 physiscal class with unilateral breast cancer who underwent breast-conserving surgery under general anesthesia, between January and Octobar 2015. All patients were premedicated with atropine and midazolam. For the prevention of acute emesis all patients got Klometol and Dexason 30 minutes before surgery.

General anesthesia: In the operating room we applied standard monitoring as electrocardiogram, noninvasive blood pressure, pulse oximetry, capnography and spectral entropy for monitoring depth of anesthesia. Anesthesia was induced with 1.5– 2.5 mg/kg propofol, and infusion of 1 mcg/kg remifentanil for 1 min, followed by 0.6 mg/kgrocuronium to facilitate laryngeal mask insertion. Anesthesia was maintained with medical air and oxygen, infusion of propofol and a fixed infusion of 0.4 mcg/kg/min of remifentanil to maintain bispectral index of 40–60. In last 30 minutes of operation in group A, with 13 patients, the dose of remifentanil was the same till the end of surgery. In group B with 12 patients, in last 30 minutes remifentanil was gradually lowered on every 10 minutes, from 0.4 to 0.1 mcg/kg/min. Patients were mechanically ventilated to maintain an end-tidal concentration of carbon dioxide between 35– 40 mmHg throughout the surgery. Muscle relaxation was achieved with 0.15 mg/ kg rocuronium.Tradamol 100 mg intravenously was administered to all patients15 minutes before end of operation. At the end of the surgery, propofol and remifentanil administration were terminated at skin closure and muscle relaxation was antagonized with i.v.atropine and neostigmine.Laryngeal mask was removed after patients' response to the verbal command and adequate spontaneous ventilation. Patients were transferred to post anesthesia care unit.

Postoperative pain treatment was consisted of application of Ketorolac.

Randomization was performed before induction of anesthesia by an independent anesthesiologist responsible for patient allocation. Patients were allocated to one of the two groups. After induction in anesthesia, patients in group A (control group constant remifentanil infusion) were maintained with 0.4 μ g/kg/min remifentanil until the end of surgery. In group B (experimental group) remifentanil was gradualy lowered in last 30 minutes (0.4 μ g/kg/min → 0.1 μ g/min) before the end of surgery.

Outcomes: Primary outcome was estimation of pain intensity after operation. Patients were asked to evaluate their level of postoperative pain at 30 min, 2 h, 6 h, 12 h, and 24 h postoperatively using visual analogue scale for pain (VAS) in rest and after arm movement in the first 24h. Secondary outcome were use of rescue analgesic in 1h and after 1h of operation.

Statystical analysis was performed by Fisher´s exact test and Wilcoxon rank sum test with continuity correction (used to test differences between groups).

3. RESULTS

All patients have average age 48.67 and average BMI 24, 20 - A group (52%), average age 49.1 and average BMI 24.07, B group (48%), average age 47.4 and BMI 24.50, ASA 2 physical class, the average duration of intervention was 81.9 min (Tabel 1.). Average value of pain with arm movement expressed by the VAS scale in the first 24 hours in the B vs A group was 2.07 vs. 4.0, $p < 0.05$. Average pain intensity in rest for B vs. A group was 1.04 vs. 3.0 with $p < 0.05$. Use of rescue analgesic in first postoperative hour for B vs A group was 1 vs 3 patients, $p<0,01$. After 1 hour of dose of rescue analgesics value of pain by VAS is B vs A group 0 vs. 0.6 with $p < 0.05$ (Tabel 2.).

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Tabel 1. BMI-Body Mass Index, OT-Operation Time, RRS-Recovery Room Stay, LOS-Length of hospital Stay

Patients details	***A group (13/25)***	***B group (12/25)***	***p***
N (%)	52	48	>0.5
BMI	24.07	24.5	>0.5
OT (min)	78.7	85.1	>0.5
RRS (min)	61	54	>0.5
LOS	2.35	2.30	>0.5

Tabel 2. AM-Arm Movement, RA-Rescue Analgesic

Pain	A group (mean VAS)	B group (mean VAS)	p
Rest	3.0	1.04	<0.05
AM	4.0	2.07	<0.05
RA (<1h)	3.0	1.0	<0.01
>1h after RA	0.6	0	<0.05

4. DISCUSSION

This study was designed to investigate whether intraoperative lowering of remifentanil could diminish pain and rescue analgesics postoperatively. The results of this study showed that gradual decrease of remifentanil at the end of the surgery significantly reduced the postoperative pain scores and the requirement of rescue analgesics.

Pain scores were higher in control group (A), with continuous remifentanil dose infusion. In experimental group (B), gradual lowering of remifentanil reduced postoperative pain score. In control group with continuous remifentanil infusion patients had a statistically significant higher mean VAS score. Probably such patients in control group developed opioid induced hyperalgesia or acute opioid tolerance. It is difficult to distinguish acute opioid tolerance and opioid induced hyperalgesia because combination of these phenomena may be due to infusion of highdose opioids. A lot of studies have shown that higher doses of opioids provoke OIH[18] and also that patients developed OT and need for higher doses of opioids postoperatively[19].

Opioid induced hyperalgesia is defined by the increased pain sensitivity whereas acute opioid tolerance is a decreased sensitivity to opioid analgesics after administration of high dose opioids[20]. Activation of the NMDA receptor and the subsequent central sensitization of nociceptive system are main causes of OIH and OT[21]. Remifentanil is different from other opioids because it directly acts on NMDA receptor[22]connecting with glycine which is bound with glutamate of the NMDA receptor during activation[23]. The present study showed that gradual dose reduction of remifentanil at the end of surgery reduced the postoperative pain.

Some authors concluded that remifentanil OIH was not apparent during propofol anesthesia compared with the effect produced during sevoflurane anesthesia even though dosage of remifentanil was increased from 1.0 to 4.0 ng/ml[24,25,26]. Propofol has some modulatory effect on OIH, through inhibition of the NMDA subtype of the glutamate receptor[27] , which is one of the potential mechanisms that induced the OIH. In this study we used propofol for maintenance of anesthesia.It is obvious that propofol did not inhibit OIH provoked

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by high doses of remifentanil, but probably inhibited or reduced the same reactions of remifentanil with lower doses.

At the end of the surgery patients received tramadol which is μ –opioid agonist, serotonin reuptake inhibitor and NMDA receptor antagonist[28]. Probably this dual manner of action of tramadol as μ –opioid agonist and NMDA receptor blocator, in combination with lower doses of remifentanil additionally reduces pain caused by OIH and OT.

Patients in control group had significantly higher pain score. In that group after intervention with rescue analgesic,ketorolac, pain relief was much better.

5. CONCLUSION

Results of this study suggested that lowering of remifentanil at the end of surgery could reduce postoperative pain and need for rescue analgesics in patients with breast conserving surgery. Combination of propofol during anesthesia and tramadol at the end of surgery reduces possibility of OIH and OT.

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