The Role of Gabapentin in Prevention of Remifentanil-Induced Hyperalgesia

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ABSTRACT:

BACKGROUND:

Remifentanil is widely used as intraoperative analgesic. Post infusion hyperalgesia has been documented experimentally in both animal and human volunteers. Gabapentin has anti-hyperalgesic effect.

OBJECTIVE:

To evaluate the effect of single preoperative oral dose of 300 mg gabapentin in attenuation of postoperative hyperalgesia induced by remifentanil and the decrease in post-operative analgesic requirement.

PATIENT AND METHOD:

A prospective randomized clinical trial conducted in Tikrit teaching hospital/ Iraq, at 2013. It involves 60 patients who underwent appendectomy. All patients were randomly allocated into two equql groups (each of 30 patients): First controlled group (CG) didn't pre-medicated with gabapentine and 2nd gabapentine group (GG) pre-medicated with gabapentin.

Intraoperative infusion of remifentanil was used & postoperative pain was assessed in all cases.

RESULTS:

The numerical analog scale NAS score and analgesia requirement post operatively was significantly higher in most times in the (CG) as compared with those of the (GG).

CONCLUSION:

Premedication with 300mg gabapentin orally decreased hyperalgesic effect induced by remifentanil and so decreased the pain score and the analgesic requirement postoperatively.

KEY WORDS: gabapentin ,remifentanil , hyperalgesia.

INTRODUCTION:

Remifentanyl is a potent ultra short-acting synthetic opioid analgesic drug. It is given to patients during surgery to relieve pain and as an adjunct to an anaesthetic.(1) Some studies showed that exposure to remifentanil cause acute hyperalgesia after a surgery.(2) Hyperalgesia means an increased response to a painful stimulus.(3) Opioid-induced hyperalgesia effects are thought to result from the central and peripheral nervous system sensitization and they share the same mechanisms with that of the hyperalgesia associated with nerve injury.(4) This suggests that preemptive treatment with drugs that are effective for the management of neuropathic pain may prevent or reduce the pain sensitization induced by opioids.(5) Gabapentin is a 2-[1-aminomethyl] cyclohexyl acetic acid], it is an anti-epileptic medication(6), and also used to treat diabetic neuropathy, postherpetic neuralgia, and reflex sympathetic dystrophy(7). It is an antihyperalgesic drug that selectively affects the nociceptive process involving central sensitization(8) The benefit of using gabapentin in the perioperative setting has been evaluated in recent studies(9). These report promising reductions in postoperative morphine consumption(10). In this study we evaluated the effect of single preoperative oral dose of 300 mg gabapentin in prevention of postoperative hyperalgesia induced by remifentanil and the decrease in analgesic requirement post-appendicectomy under general anesthesia.

PATIENTS & METHOD:

A prospective randomized Clinical trial conducted in Tikrit teaching hospital / Iraq from 23-1-2013 to 30-4-2013. It involved 60 (15-55) years old patients who were class I & II physically state American Society of Anesthesia (ASA) classification who undergone appendectomy by grid iron incision under general anesthesia.

Contraindication to any of drugs used in the study, history of any chronic pain, chronic opioids use within 3 months before surgery, or drug or alcohol addiction were excluded from the study. Consents were taken from all patients.

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All patients were randomly allocated into two equal group (each of 30 patients): First controlled group (CG) didn't receive gabapentine premedication and 2nd gabapentine group (GG) received gabapentin 300 mg orally one hour before surgery.

Demographic data :age, weight, and gender were recorded. Standard anesthesia was conducted for all patients by given metoclopromide0.1mg/kg, dexamethasone 8mg, midazolam0.02mg/kg and thiopental 3-5 mg/kg (anesthetizing dose), bolus dose of 0.5 mic/kg remifentanil, and suxamethonium 1 mg/kg. All patients were endotrachially intubated and mechanicaly ventilated .General anesthesia was maintained with isoflurane 0.8-1.2 concentration, atracurium 0.3 mg/kg, and remifentanil 0.05-0.15 mic/kg/min according to the patient's vital signs. all patients received tramadol 1mg/kg and diclofenac sodium 75 mg i.m for postoperative pain relief.

At the closure of skin, remifentanil and isoflurane were discontinued. Neuromuscular blockade was antagonized by atropine 1mg and neostigmine 2.5 mg, and then endotracheal tubes were extubated. The durations of anesthesia were recorded. All patients were monitored by pulse oximetry, electrocardiography (ECG) and noninvasive blood pressure (BP)

All patients were transferred to the post anesthetic care unit (PACU) and postoperative pain was monitored after complete awaking and

15 minute later by numerical analogue score (NAS) from (0-10): 0 means no pain and 10 means worst imaginable pain. When NAS was more than 3, pain controlled by given i.v tramadol 0.25mg/kg, which if NAS was still more than 3 repeated once after 10 minutes, if NAS was still more than 3 morphine 0.02 mg/kg was given.

In the ward postoperative pain was assessed by NAS at specific time intervals: 1, 3, 6, 9, and 12 hours postoperatively, when NAS more than 3, paracetamol i.v infusion 1 gm was given and recorded.

The Statistical Package for Social Sciences (SPSS) version 18 was used for data entry and analysis. Chi (X2) square test and Student t test were used to analyze data and were regarded as statistically significant when P value of ≤ 0.05.

RESULTS:

The sex distribution shows that 15(50%) of (GG) are male and 15(50%) are female, in comparison to 12(40%) of (CG) are male and 18(60%) are female, this variation was not significant.

The mean age among (GG) was 27±6.9 versus 28.1±8.5 among (CG), the weight among (GG) was 64.6±7.4 in comparison to 64.9 ±8.4 for (CG), and the duration of surgery among (GG) was 39.9±7.3, versus 42.2±4.9 in (CG), all these variation was statistically not significant.

The numerical analogue score at recovery after complete awaking shows that the mean value was 2.6±0.7 among (GG) in comparison to 4.1±0.5 in (CG) , the numerical analogue score at recovery after 15 minutes, shows that the mean value was 5.2±0.6 among (GG) in comparison to 6.7±1.02 in (CG) , these variation were statistically significant, as shown in table (1)

Table 1: Mean numerical analogue score at recovery.

Numerical Analogue Score at recovery	Subject distribution	N	Mean	Std. Deviation	P value
NAS at Complete awareness	GG	30	2.6	0.7	<0.05 S
	CG	30	4.1	0.5	
NAS after 15 minutes	GG	30	5.2	0.6	<0.05 S
	CG	30	6.7	1.02	

The mean doses of analgesia that needed was as following : First dose of Tramadol was 15.7±1.6 among (GG) as compared with 16.5±2.3 in (CG) this variation wasn't significant. The 2nd dose of Tramadol was 11.59±7.5 among (GG) as compared with 16.5±2.3 in (CG) this variation was statistically significant. The Morphine dose of Tramadol among (GG) was 0.55±0.9 as compared with 0.9±0.7 in (CG) this variation wasn't significant as shown in table (2).

Table 2: Mean dose of analgesic drugs needed.

Dose of analgesia	Subject classification	Number	Mean	Standard deviation	P value
1st dose Tramadol	(GG)	30	15.7	1.6	>0.0 NS
	(CG)	30	16.5	2.3	
2nd dose of Tramadol	(GG)	30	11.59	7.5	<0.05 S
	(CG)	30	16.5	2.3	
Morphine Dose	(GG)	30	0.55	0.9	>0.0 NS
	(CG)	30	0.9	0.7	

Table (3) shows the results of NAS at ward, the NAS after 1hr among (GG) was 3±1.1 in comparison to 3.4±0.9, this variation was statistically not significant, while all other times (3,6,9, and 12) were significant.

Table 3: Mean NAS score according to time at floor according.

NAS score at floor	Subject distribution	N	Mean	Std. Deviation	P value
NAS after 1 hr	(GG)	30	3	1.1	>0.0 NS
	(CG)	30	3.4	0.9	
NAS after 3 hr	(GG)	30	2.4	0.9	<0.05 S
	(CG)	30	3.4	0.7	
NAS after 6 hr	(GG)	30	1.8	0.8	<0.05 S
	(CG)	30	2.5	0.7	
NAS after 9 hr	(GG)	30	1.1	0.3	<0.05 S
	(CG)	30	1.8	0.4	
NAS after 12 hr	(GG)	30	0.8	0.4	<0.05 S
	(CG)	30	1	0	

The Paracetamol infusion need among (GG) and controls show that 15(50%) of cases needed infusion, in comparison to 18(60%) of (CG), the odds ratio for paracetamol infusion was 0.66,this variation was not significant as shown in table (4).

Table 4: The Pracetamol Infusion distribution among both groups.

Pracetamol Infusion			Subject distribution (GG)	Subject distribution (CG)	Total	P value
	yes	No.	15	18	33	
		%	50.0%	60.0%	55.0%	>0.05 NS
	No	No.	15	12	27	
		%	50.0%	40.0%	45.0%	
Total		No.	30	30	60	
		%	100.0%	100.0%	100.0%	

DISCUSSION:

The result in this study was NAS after full awareness in the recovery for GG group (2.6±0.7) while NAS for CG group was (4.1±0.5) which is significantly higher and NAS after 15 minute for GG group(5.2±*0.6)* and for CG group (6.7±1.02) which is significant higher. and tramadol 1st dose requirement was(15.7±*1.7)* in the CG group as compared with(16.5±*2.3)* in GG group and tramadol 2nd dose (11.59±7.5) in CG group compared with (16.5±2.3) in GG group which is significant higher in the first 12 hours post operatively. This result show that NAS and analgesic requirement significantly higher in CG group as compaired with GG group.

Christophe Ménigaux and colleagues [(11)] studied gabapentin on forty patients randomly assigned to receive 1200 mg oral gabapentin or placebo 1–2 h before surgery; anesthesia was standardized with remifentanil infusion 0.05 mic/kg/min. Patients received morphine, 0.1 mg/kg, 30 min before the end of surgery and postoperatively via a patient-controlled pump. The gabapentin group required less morphine than the control group (29 ± 22 mg versus 69 ± 40 mg, respectively; P < 0.001).

Visual analog scale pain scores at rest and after mobilization were significantly reduced in the gabapentin group. They concluded that premedication with 1200 mg gabapentin improved postoperative analgesia, and early knee mobilization after arthroscopic anterior cruciate ligament repair. Although we used quarter their dose of gabapentin, our findings are thus consistent with previous results.

Also in another study, Pandey CK and colleagues (12)evaluated the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar diskectomy. placebo-controlled study in 100 patients who were divided into five groups to receive placebo or gabapentin 300, 600, 900, or 1200 mg 2 hours before surgery. After surgery, patients were transferred to the post-anesthesia care unit (PACU). Patients received patient-controlled analgesia (fentanyl 1.0 µg/kg on each demand with lockout interval of 10 minutes); total fentanyl consumption during initial 24 hours was recorded. Patients who received gabapentin 300 mg had significantly lower VAS score at all time points. They consumed less fentanyl (patients who received placebo processed. Patients who received gabapentin 600, 900, and 1200 mg had lower VAS scores at all time points than patients who received gabapentin 300 mg . Increasing the dose of gabapentin from 600 to 1200 mg did not decrease the VAS score, nor did the increasing dose of gabapentin significantly decrease fentanyl consumption. Although we studied single dose of gabapentine, 300 mg, our findings in this regard were consistent with these results.

Hyong Rae Jo and colleagues [13] studied sixty patients who were scheduled for total abdominal hysterectomy were randomly allocated into 3 groups. The 1st received a placebo as premedication and an intraoperative saline infusion (control group), the 2nd received a placebo as premedication and an intraoperative infusion of remifentanil at a rate of 3-4 ng/ml (remifentanil group), & the 3rd received pregabalin 150 mg as premedication and an intraoperative infusion of remifentanil at a rate of 3-4 ng/ml (pregabalin-remifentanil group). Postoperative pain was controlled by titration of fentanyl in the postanesthetic care unit (PACU), followed by patient-controlled analgesia (PCA) with fentanyl. The patients were evaluated over the 48 hours postoperative period. The result was the fentanyl titration dose given in the PACU was significantly larger in the remifentanil group as compared with those of the other two groups. At rest, the VAS pain score in the remifentanil group at 2 h after arrival in the PACU was significantly higher than those in the other two groups. Our findings are thus consistent with these results.

During surgery in the present study, we used remifentanil, which can induce postoperative opioid hyperalgesia [14], increase NAS score, and analgesic dose required to achieve satisfactory pain relief. Our results revealed that premedication with 300 mg oral gabapentin reduced postoperative analgesic and morphine consumption and it reduced the higher pain intensity induced by remifentanil. This suggested that gabapentin may be useful in patients with pain sensitization induced by opioids.

There has been a report showing that perioperative administration of gabapentin was associated with a higher incidence of dizziness, blurred vision and headache during the first 24 h after surgery [15], but gabapentin 300 mg did not increase any side effects or the recovery times in our results. Although the analgesic requirement in the PACU was significantly higher in the controlled group, there were no significant differences of the opioid-related adverse effects, including postoperative nausea and vomiting (PONV). One explanation would be that all the patients were given an injection of IV metoclopramide and dexamethasone before the induction of anesthesia.

CONCLUSION :

Premedication with 300mg gabapentin orally decreased hyperalgesic effect induced by remifentanil and so decreased the pain score and the analgesic requirement postoperatively.

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