Intravenous patient controlled analgesia in thyroid surgery : Comparison of three regimens using fentanyl and ketorolac

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Intravenous patient controlled analgesia in thyroid surgery : Comparison of three regimens using fentanyl and ketorolac

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<ABSTRACT>

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After thyroidectomy, patients have moderate pain that need opioid treatment and they usually have nausea or vomiting. Intravenous patient controlled analgesia (i.v. PCA) with opioid can control postoperative pain well, but it can cause nausea or vomiting. But NSAIDs, through a synergistic action with opioids, can reduce these systemic side effects. The aim of this study was to compare the analgesic efficacy and side effects of three PCA regimens using fentanyl and ketorolac and to determine the appropriate dosage of fentanyl and ketorolac in thyroid surgery. One hundred and thirty-five patients undergoing elective thyroidectomy were randomly divided into three PCA groups. : Group I

(n=45), fentanyl 15 μg/kg + ondansetron 12 mg, Group II (n=45), fentanyl 12.5 μg/kg + ketorolac 1.5 mg/kg + ondansetron 12 mg, Group III (n=45), fentanyl 10 μg/kg + ketorolac 3 mg/kg + ondansetron 12 mg. Drugs of each group were mixed with normal saline in a total volume of 100 ml. Basal infusion rate was 2 ml/hr and the lockout interval was 15 mins with the bolus dose of 0.5 ml. After the specimen was removed, i.v. PCA was connected. Pain scores, nausea and vomiting and other side effects were assessed at postoperative 1, 6, 12 and 24 hrs respectively. Pain scores were similar among three groups. But postoperative nausea and vomiting (PONV) was significantly lower in groups II and III ($p < 0.05$) compared with group I. Postoperative dizziness was significantly lower in group III compared with groups I and II ($p < 0.05$). We conclude that i.v. PCA with fentanyl 10 μg/kg, ketorolac 3 mg/kg and ondansetron 12 mg causes minimal side effects such as PONV and dizziness in thyroid surgery.

Key words : fentanyl, ketorolac, pain, PCA, PONV, thyroid surgery

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I. INTRODUCTION

One of the most common methods for providing postoperative analgesia is via patient-controlled analgesia (PCA). It has been used since the late 1960s.[1] Nowadays it is used not only in major surgery but also in minor surgery for post operative pain control. PCA reduces analgesics requirements and it increases patient satisfaction and progress after surgey.[2,3]

Although thyroid surgery is a short-stay procedure, pain after thyroid surgery is expected to be moderate.[4,5] It has been reported that the mean postoperative pain score was 6.9 on a visual analog scale (VAS) from 1 to 10 and 90% of the patients required morphine during the first postoperative day.[6] Other studies have reported the need for opioid analgesia at least in the early postoperative

period.[7-9] Besides, thyroid surgery carries a major risk of nausea and vomiting because it is a cervicofacial surgery performed mainly in women.[10,11] Therefore, after thyroid surgery, it is important to control pain and reduce nausea and vomiting.

Opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) are used in postoperative pain control. Opioids can increase postoperative nausea and vomiting and other side effects, such as sedation, dizziness, urinary retention and pruritus.[12] But NSAIDs, through synergistic action with opioids,[13-16] can reduce these systemic side effects.[17,18] In thyroid surgery, use of NSAIDs like ketoprofen reduced the pain score as well as morphine requirements and related side effects such as nausea and vomiting.[19] And the addition of ketoprofen improved analgesia in patients who received intraoperative fentnyl.[20]

Many studies reported about postoperative pain control ways, such as local anesthetic wound infiltration,[6,21] bilateral superficial cervical plexus block[7,22,23] and greater occipital nerve block[24] in thyroid surgery. But the efficacy of intravenous PCA (i.v. PCA) in thyroid surgery has not yet been assessed. The aim of this study was to compare the analgesic efficacy and side effects of three PCA regimens using fentanyl and ketorolac and to determine the appropriate dosage of fentanyl and ketorolac in thyroid surgery.

II. MATERIALS AND METHODS

1. MATERIALS

This study was approved by Yonsei University, Medical School Review Board for human investigation and written informed consent was obtained from all patients (including the preliminary study). One hundred thirty-five patients who were ASA physical status I-II, female patients aged 20-60 yr and scheduled for elective thyroid surgery due to thyroid cancer were enrolled in this study. Thyroid surgery was performed by the same surgeon with a similar surgical technique and surgical drains. All patients were euthyroid state at the time of surgery. Patients were excluded if they had renal failure, bleeding tendency, a known allergy or any contraindication to the use of NSAIDs.

2. METHODS

We considered PONV as the primary outcome, and assumed the incidence of PONV to be approximately 50% in Group I (many studies had shown the incidence of opioid-induced emesis in the post-surgical setting to range between 10% and 50%[25-27]) and 25% in group II, III (a reduction of nausea and vomiting from 50% to 25% was considered as clinical importance[11,28]). Thus, the sample size of 45 patients in each group provided 80% power at the 95% level of significance.

Using a random number sequence, patients (n=135) were randomly divided into three PCA groups : Group I (n=45), fentanyl citrate (Fentanyl®, Ha Na

Pharm, Seoul, Korea) 15 μg/kg + ondansetron (Onseran®, Yuhan, Seoul, Korea) 12 mg, Group II (n=45), fentanyl 12.5 μg/kg + ketorolac tromethamine (Tarasyn®, Roche Korea, Seoul, Korea) 1.5 mg/kg + ondansetron 12mg, Group III (n=45), fentanyl 10 μg/kg + ketorolac 3 mg/kg + ondansetron 12mg. Drugs of each group were mixed with normal saline in a total volume of 100 ml. The regimen was based on the study that 60 mg of ketorolac and 100 mg of fentanyl was equianalgesic[29] and on Food and Drug Administration (FDA) recommendation that total daily dose of injectable ketorolac is 120 mg. Basal infusion rate was 2 ml/hr and the lockout interval was 15 mins with the bolus dose of 0.5 ml.

Patients were premedicated with midazolam 0.04 mg/kg i.m. 30 minutes before surgery. General anesthesia was induced with remifentanil 1 μg/kg and propofol 1-2 mg/kg. Orotracheal intubation was done after administration of rocuronium bromide 0.8 mg/kg. Anesthesia was maintained with remifentanil 0.05-0.15 μg/kg/min and 1.5-2% end tidal sevoflurane in 50% O_2/air. After the specimen was removed, i.v. PCA (Accufuser Plus®, P2015M, Woo Young Medical, Korea) was connected. At the time of skin suture, ondansetron 4 mg was injected. No other analgesics and dexamethasone were given during operation.

The assessment of pain and side effects such as nausea and vomiting, sedation, dizziness, urinary retention and pruritus were made at postoperative 1, 6, 12 and 24 hrs. Pain was evaluated by 11-point numerical rating scale (NRS). Patients

were instructed preoperatively to express their pain on the 0-10 NRS, where 0 meant no pain at all and 10 represented the worst pain imaginable. Nausea and vomiting were graded on a four point scale as 0 = no nausea, 1 = mild nausea, 2 = severe nausea which needs anti-emetics, 3 = retching and/or vomiting. Grades 3 and 4 were grouped together as postoperative nausea and vomiting (PONV). We recorded sedation score on a four point scale as 0 = awake, 1 = mild, 2 = sleepy but awakable, 3 = very sleepy. When patients wanted more pain control, further injection of fentanyl 50 μg or ketorolac 30 mg were allowed. The patients of PONV group (grade 2 and 3) were given antiemetics, metoclopramide 10 mg or ondansetron 4 mg. When patients didn't want PCA because of side effects, PCA was locked for a while or removed.

Statistical analysis was performed using SPSS 12.0 (SPSS Inc., Chicago, IL, USA). Parametric data (age, weight, BMI, duration of operation, pain scores) were analyzed using one-way ANOVA. The nausea and vomiting were compared using Kruskal-Wallis test. If the test proved significant, a Mann-Whitney U test with Bonferroni correction was used to evaluate differences between groups. Discrete variables (history of motion sickness, PONV, PCA removal, other side effects) were analyzed with Chi-square test. All values were presented as means ± standard deviation (SD) or percentage. A p value < 0.05 was considered as statistically significant.

III. RESULTS

A total of 135 patients (45 in each group) completed the protocol. There were no differences in patients characteristics among three groups (Table 1).

Table 1. Patients characteristics

	Group I (n = 45)	Group II (n = 45)	Group III (n = 45)
Age (yrs)	47.0 ± 7.0	47.5 ± 8.1	50.3 ± 7.5
Weight (kg)	58.9 ± 7.7	60.2 ± 7.3	61.5 ± 8.4
BMI (kg/m^2)	23.9 ± 2.9	24.1 ± 2.7	25.2 ± 3.9
History of motion sickness	7 (15.6%)	7 (15.6%)	8 (17.8%)
Duration of operation (mins)	126 ± 33	118 ± 20	121 ± 20

Values are mean ± SD or number of patients (percentage).
Group I : fentanyl 15 μg/kg + ondansetron 12 mg; Group II : fentanyl 12.5 μg/kg + ketorolac 1.5 mg/kg + ondansetron 12mg; Group III : fentanyl 10 μg/kg + ketorolac 3 mg/kg + ondansetron 12mg. No significant differences among three groups.
BMI = body mass index.

Postoperative pain scores were similar among three groups (Figure 1). Nausea grades were significantly lower in Group III compared with Group I at postoperative 1 hr ($p < 0.05$). And it were significantly lower in Group II and III compared with Group I at postoperative 6, 12 and 24 hrs ($p < 0.05$). But nausea grades were not different between Group II and III (Table 2).

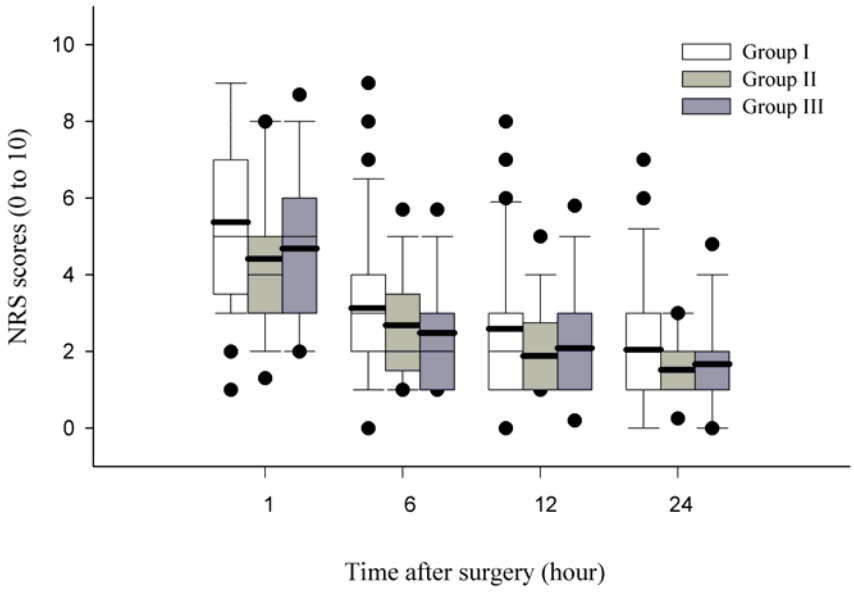

Figure 1. Numerical rating scale (NRS) for pain during postoperative period. Box plot with median (solid line), mean (bold line), 25th-75th percentiles (box), and 10th-90th percentiles (whiskers). Outliers are indicated by the solid circles. Group I was received i.v. PCA with fentanyl 15 μg/kg and ondansetron 12 mg. Group II was received i.v. PCA with fentanyl 12.5 μg/kg, ketorolac 1.5 mg/kg and ondansetron 12mg. Group III was received i.v. PCA with fentanyl 10 μg/kg, ketorolac 3 mg/kg and ondansetron 12mg. No significant differences among three groups.

Table 2. Postoperative nausea grades in three groups

		Group I	Group II	Group III
1 hr†				
Grade	0	26	31	35
	1	5	7	4
	2	13	7	6
	3	1	0	0
6 hr*†				
Grade	0	19	31	37
	1	10	8	4
	2	10	4	3
	3	5	2	1
12 hr*†				
Grade	0	19	32	37
	1	12	6	3
	2	4	1	1
	3	6	5	2
24 hr*†				
Grade	0	22	36	35
	1	6	3	4
	2	5	3	3
	3	5	2	1

Group I : fentanyl 15 μg/kg + ondansetron 12 mg; Group II : fentanyl 12.5 μg/kg + ketorolac 1.5 mg/kg + ondansetron 12mg; Group III : fentanyl 10 μg/kg + ketorolac 3 mg/kg + ondansetron 12mg.
Grade was : 0 = no nausea, 1 = mild nausea, 2 = severe nausea which needs anti-emetics, 3 = retching and/or vomiting.
*Significant difference at $p < 0.05$ between Group I and II.
†Significant difference at $p < 0.05$ between Group I and III.
After locking or removal of PCA, we didn't check nausea grades of patients. So total number of patients was different on times.

Incidence of PONV was lower in Group II (33.3%) and III (28.9%) compared with Group I (57.8%) during postoperative 24 hrs ($p < 0.05$). But it was not different between Group II and III. The proportion of patients who wanted locking or removal of PCA was higher in Group I (31.1%) compared with Group II (8.9%) and III (11.1%) ($p < 0.05$). But it was not different between Group II and III (Figure 2).

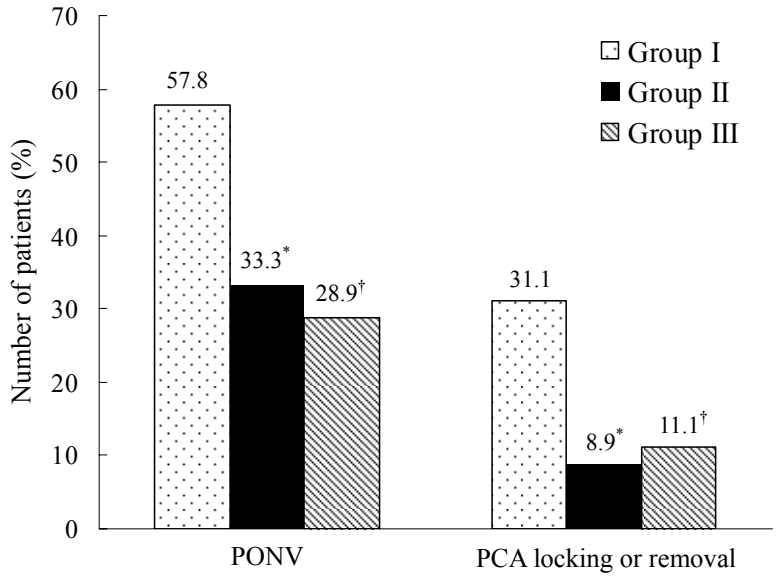

Figure 2. Incidence of postoperative nausea and vomiting (PONV) and locking or removal of PCA during postoperative 24hrs. Nausea grade 2 and 3 were grouped together as PONV. Group I was received i.v. PCA with fentanyl 15 μg/kg and ondansetron 12 mg. Group II was received i.v. PCA with fentanyl 12.5 μg/kg, ketorolac 1.5 mg/kg and ondansetron 12mg. Group III was received i.v. PCA with fentanyl 10 μg/kg, ketorolac 3 mg/kg and ondansetron 12mg. *Significant difference at $p < 0.05$ between Group I and II in PONV and PCA locking or removal. †Significant difference at $p < 0.05$ between Group I and III in PONV and PCA locking or removal.

No difference was noticed with regard to sedation (Table 3). Sedation score 3 was never seen in all groups. And sedation score 2 was never seen in Group III.

Table 3. Postoperative sedation scores in three groups

		Group I	Group II	Group III
1 hr				
Score	0	39	37	38
	1	6	8	7
	2	0	0	0
	3	0	0	0
6 hr				
Score	0	33	39	36
	1	11	5	9
	2	1	1	0
	3	0	0	0
12 hr				
Score	0	30	41	40
	1	11	3	3
	2	0	0	0
	3	0	0	0
24 hr				
Score	0	29	37	39
	1	8	7	4
	2	1	0	0
	3	0	0	0

Group I : fentanyl 15 μg/kg + ondansetron 12 mg; Group II : fentanyl 12.5 μg/kg + ketorolac 1.5 mg/kg + ondansetron 12mg; Group III : fentanyl 10 μg/kg + ketorolac 3 mg/kg + ondansetron 12mg.
Scoring was : 0 = awake, 1 = mild, 2 = sleepy but awakable, 3 = very sleepy.
No significant differences among three groups.
After locking or removal of PCA, we didn't check sedation score of patients. So total number of patients was different on times.

Incidence of other side effects is shown in Figure 3. Dizziness was significantly lower in Group III (11.1%) compared with Group I (40.0%) and II (28.8%) ($p < 0.05$). But Group I and II was not different in dizziness. There were no differences in pruritus and bladder distension between three groups.

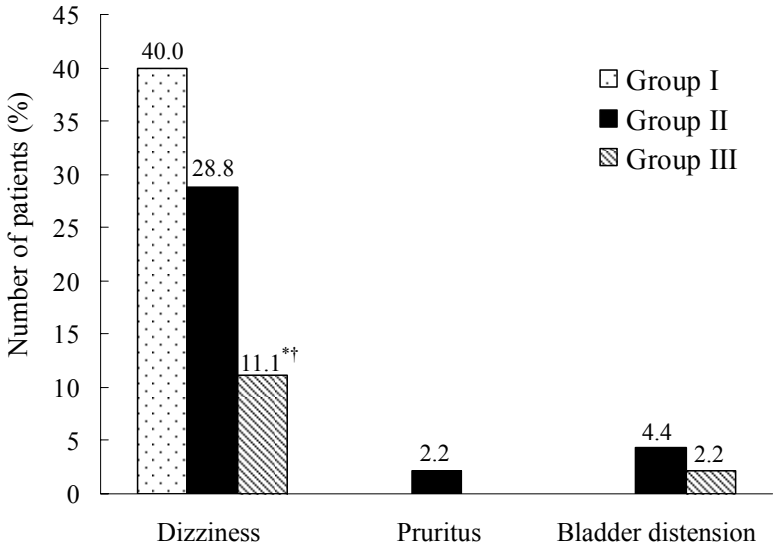

Figure 3. Incidence of other side effects during postoperative 24hrs. Group I was received i.v. PCA with fentanyl 15 μg/kg and ondansetron 12 mg. Group II was received i.v. PCA with fentanyl 12.5 μg/kg, ketorolac 1.5 mg/kg and ondansetron 12mg. Group III was received i.v. PCA with fentanyl 10 μg/kg, ketorolac 3 mg/kg and ondansetron 12mg. Significant difference at $p < 0.05$ between Group I and III in dizziness. †Significant difference at $p < 0.05$ between Group II and III in dizziness.

IV. DISCUSSION

The benefits of i.v. PCA compared with intermittent i.m. injection of opioids have been best summarized in two published systemic reviews.[30,31] Both of these evidence-based reviews concluded that i.v. PCA offers better analgesic efficacy as well as superior patient satisfaction. With intermittent bolus administration, there are frequent periods with the concentration more than and less than the target analgesic concentration. In contrast, PCA results in the opioid concentration being in the target range for a large percentage of time.[32]

After thyroid surgery, most patients require effective postoperative analgesia. The causes of pain are a cervicotomy itself, an operative cervical hyperextension that causes postoperative muscular cervicalgia[33] and an orotracheal intubation that causes postoperative irritation and laryngeal discomfort projecting into the operated region.[34] Postoperative discomfort can also be increased by the cervical drains, which are kept in place for 24 hours.[10]

In our study, patients complained of pain at the incision site, sore throat, posterior neck pain and headache. Pain at the incision site and sore throat were the most common complaints. Also the most common headache was an occipital headache. Gozal et al.[6] and Bagul et al.[21] reported that bupivacaine wound infiltration reduced postoperative pain and opioid demand in thyroid surgery. Han et al.[24] reported that greater occipital nerve block with bupivacaine reduced occipital headache and posterior neck pain after thyroid surgery. These studies focused on the efficacy of regional techniques. However, the

mechanism of pain after thyroidectomy is complex, so we need other general pain control methods. Because i.v. PCA controls pain in a systemic manner, it would control complex pains in thyroid surgery. As a preliminary study, we estimated the pain of 30 patients who did not receive i.v. PCA after thyroidectomy. The mean postoperative numerical rating scale (NRS, 0-10) of these patients was 6.7 at 1 hr, 4.8 at 6 hrs, 3.9 at 12 hrs and 2.6 at 24 hrs. It was significantly higher than that of the PCA group of our study ($p < 0.05$).

Postoperative nausea and vomiting (PONV) is the most common and most bothersome side effect of i.v. PCA. Certain surgical procedure, drugs used during anesthesia, pain, anxiety and dehydration are all associated with an increased incidence of PONV.[35] Therefore thyroid surgery and opioid-based i.v. PCA can increase the incidence of PONV. Sonner et al.[11] reported the incidence of PONV was 54% in thyroid surgery. In our study, the incidence of PONV was 33.3% in Group II and 28.9% in Group III. So i.v. PCA with opioid and ketorolac did not increase the incidence of PONV.

Morphine remains the "gold standard" for i.v. PCA, as the most studied and most commonly used i.v. PCA drug in the United States.[36] But morphine has an active metabolite−morphine-6-glucuronide(M6G)−that also induces analgesia, sedation, and respiratory depression. Whereas morphine is eliminated mainly by glucuronidation, its active metabolite relies predominantly on renal excretion for elimination. Prolonged and profound delayed onset respiratory depression has been reported in patients with renal failure receiving parenteral morphine.[37]

Fentanyl is a good alternative for morphine-intolerant patients or those with altered renal function because it does not rely on renal excretion for elimination. Because of its lipophilicity, fentanyl has a quicker onset than morphine, so it makes fentanyl better suited for i.v. PCA. Fentanyl has been used successfully for i.v. PCA.[38,39] Therefore, fentanyl would be more suitable than morphine in a short duration of surgery like a thyroidectomy.

NSAIDs such as ketorolac inhibit the synthesis of prostaglandins both in the spinal cord and at the periphery, thus diminishing the hyperalgesic state after a surgical trauma.[40] The analgesic synergy of NSAID-opioid combination was first demonstrated by McQuay et al..[14] And the efficiency of NSAIDs in thyroid surgery also has been assessed in several studies.[19,20] In our study, the pain scores of the NSAIDs added groups (Group II and III) were similar to that of the fentanyl only group (Group I) (Figure 1). But PONV was significantly lower in the NSAIDs added groups (Group II and III) (Figure 2). Therefore, the addition of NSAIDs in an opioid-based i.v. PCA can reduce PONV in thyroid surgery.

Twenty three patients from among 135 patients wanted locking or removal of the PCA (Figure 2). The reasons were severe nausea or vomiting in 21 patients and dizziness in 2 patients. Dizziness was significantly lower in Group III compared with Group I and II (Figure 3). Therefore more NSAIDs added group (Group III) had a lower incidence of both PONV and dizziness.

Hematoma of the thyroid lodge requiring surgical investigation is relatively

rare, with an incidence of 0.5% to 1.5%.[41-43] NSAIDs administration may theoretically increase the postoperative bleeding risk[44] and thus the risk of compressive cervical hematoma. This is linked to the modifications of the coagulation system caused by treatment even of a very short duration. Although a retrospective study has shown an increase in perioperative bleeding and wall hematomas in patients treated for long periods with NSAIDs,[45] prospective studies have not shown an increase in the risk of postoperative hemorrhage with treatments lasting less than five days and started during or after the operation.[18,46,47] In our study, no cases of hematoma occurred.

The 5-HT_3 receptor antagonists are highly specific and selective for nausea and vomiting. Members of this group exert their effects by binding to the 5-HT_3 receptor in the chemoreceptor trigger zone and at vagal afferents in the gastrointestinal tract. Ondansetron was the first member of this group to be marketed in the USA and was the most widely studied. It is most effective when given at the end of surgery.[48,49] The recommended dose for prophylaxis is 4 to 8 mg i.v. in adults.[50] Therefore we mixed ondansetron 12 mg in the i.v. PCA and ondansetron 4mg was injected at the time of skin closure.

V. CONCLUSION

Intravenous PCA with fentanyl 10 μg/kg, ketorolac 3 mg/kg and ondansetron 12 mg causes minimal side effects such as PONV and dizziness in thyroid surgery.

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< ABSTRACT(IN KOREAN)>

갑상선절제술 후 fentanyl과 ketorolac을 이용한 정맥 자가통증조절시 적절한 용량

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갑상선 절제술을 받은 환자들은 술 후 아편양제제가 필요할 정도의 중증도의 통증을 경험하게 되며 다수에서 구역 또는 구토를 경험하게 된다. 아편양제제를 혼합한 정맥 자가통증조절은 술 후 통증 조절에 효과적이나 구역 또는 구토를 유발할 수 있다. 본 연구의 목적은 갑상선 수술 환자를 대상으로 fentanyl과 ketorolac의 용량 비율을 변화시켜 통증조절의 정도와 구역, 구토 등의 부작용을 비교함으로써 갑상선 수술에 적절한 정맥 자가통증조절의 용량을 조사하는 데 있다. 갑상선 절제술을 받는 135명의 환자를 세 군으로 무작위 분류하여 I군(n=45)은

fentanyl 15 μg/kg + ondansetron 12 mg, II군(n=45)은 fentanyl 12.5 μg/kg + ketorolac 1.5 mg/kg + ondansetron 12 mg, III군(n=45)은 fentanyl 10 μg/kg + ketorolac 3 mg/kg + ondansetron 12 mg을 생리식염수와 혼합하여 100 ml 정맥 자가통증조절 장치를 갑상선 조직이 제거된 직후 연결하였다. 기본 투여량 2 ml/hr, 환자 요구량 0.5 ml, 폐쇄 간격 15분으로 정하였다. 술 후 1, 6, 12, 24시간에 통증의 정도와 구역 및 구토, 다른 부작용 등을 평가하였다. 세 군에서 술 후 통증의 정도는 비슷하였다. 그러나 술 후 구역 및 구토는 I군에 비해 II와 III군에서 의미있게 낮았고($p < 0.05$), 어지러움은 I, II군에 비해 III군에서 통계적으로 의미있게 낮았다($p < 0.05$). 결론적으로, 갑상선 수술에서 fentanyl 10 μg/kg, ketorolac 3 mg/kg과 ondansetron 12 mg을 혼합한 정맥 자가통증조절을 사용하면 술 후 구역, 구토 및 어지러움을 최소화 할 수 있다.

핵심되는 말 : fentanyl, ketorolac, 통증, 자가통증조절, 수술 후 구역 구토, 갑상선수술