Original Article

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Efficacy of multimodal pain management in patients undergoing hip replacement in a Vietnamese hospital

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Abstract

An effective pain relief after hip replacement is necessary to ensure an expected surgery outcome. Multimodal pain management has been recently applied at Thong Nhat hospital, Vietnam. The objectives of this study were to evaluate the effectiveness of multimodal regimen, compared with conventional regimen in patients undergoing hip replacement. A retrospective cohort study was conducted by using medical records of patients undergoing hip replacement. Patients with renal failure and a history of drug addiction or allergy to any study medications were excluded. Patients were randomized into two groups – conventional pain control and multimodal pain control (n = 40 each group). Multimodal pain regimen included intravenous paracetamol 1-2 hours before surgery, spinal anesthesia during surgery and at least two analgesic drugs after surgery. Pre-operative intravenous paracetamol was not performed in the conventional group. There were no significant differences between two study groups with respect to baseline characteristics. Patients in multimodal pain control group had a significantly lower rate of severe pain in the first 3 days after surgery ($p \leq 0.001$), a significantly lower rate of sleep disturbance ($p = 0.003$), significantly earlier ambulation ($p = 0.001$), and a significantly lower average dose of used opioid ($p = 0.023$), compared with those in conventional group. There were no significant differences in hospital stay and adverse event rates ($p > 0.05$). The multimodal analgesic regimen provided an effective pain relief, an earlier functional recovery as well as decreased opioid consumption.

Keyword: Multimodal pain management, hip replacement, VAS, surgery.

1. INTRODUCTION

Hip replacement is one of the most common surgical interventions among orthopedics and the number of patients undergoing hip replacement is continuously increasing. However, it is an invasive procedure that causes much pain. The result of uncontrolled pain includes inability to actively participate in rehabilitation program, delayed recovery and prolonged hospitalization. Immobilization due to post-operative pain also leads to other complications such as paralytic ileus, venous thromboembolism and pneumonia. Therefore, an effective pain relief is needed to ensure an expected surgery outcome. In fact, many patients still experienced severe pain after surgery when using conventional pain control, which targets only one aspect of pain perception.

In order to solve this problem, based on a better understanding of the complexity of pain, the concept of multimodal pain management was introduced by Wall [1] in 1988. The principle of multimodal therapy is to use drugs with different mechanisms, targeting several steps of the pain pathway, taking advantages of the synergistic effect while requiring lower total dose of each agent. This method promotes more effective pain relief with fewer side effects. Since it was first introduced, multimodal pain management has received increasing interest in literature. However, many of those studies

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did not mention the role of multi-timing of pain control which, according to Parvataneni[2], is one of the most important characteristics of multimodal pain management. Meanwhile, true multimodal regimen emphasizes the role of pre-emptive analgesia, which was used before surgery. Pre-operative pain control is the key to this multimodal regimen because it prevents sensitization of the nervous system to subsequent stimuli that could amplify pain.

Although multimodal pain management was introduced long time ago with promising research results, it was carefully applied recently in Vietnamese hospitals. In Vietnam, the comparison data between conventional and new multimodal pain regimens have been lacking. In the very first study in Vietnam, Lam et al.[3] showed that the rate of patients in conventional pain relief after surgery suffered from severe pain in POD 1-3 significantly higher than those in new multimodal pain treatment group. The efficacy of multimodal pain treatment is promising in Vietnamese patients.

Therefore, the aim of this study was to evaluate the effectiveness of this multimodal regimen (comprise pre-emptive analgesia), compared with conventional regimen (without pre-emptive analgesia).

2. MATERIALS AND METHODS

2.1. Study settings

This was a retrospective cohort study using medical records of patients undergoing hip replacement at Thong Nhat hospital. The protocol of this study was approved by the Institutional Review Board of the Thong Nhat hospital (Project Number: 169 IRB/ QD-BVTN 07042015)

2.2. Inclusion criteria

- Patients undergoing hip replacement from January 1st, 2012 to June 30th, 2015

2.3. Exclusion criteria

- Patients with diagnose of renal failure and creatinine level higher than 1.5 mg/dL.
- Patients with a history of drug addiction (using more than 30 mg/day morphine or equivalent dose of opioid within a month).
- Patients who allergic to any study medications.

2.4. Sample size

A required sample size for each group was calculated using the formula:

$$n = \frac{(z_{\frac{\alpha}{2}}\sqrt{2\bar{p}\,(1-\bar{p})} + z_{\beta}\sqrt{p_1(1-p_1) + p_2(1-p_2)})^2}{\Delta^2}$$

With $\bar{p} = \frac{p_1+p_2}{2}$ and $\Delta = p_1 - p_2$

p_1, p_2 are rates of patients suffered from severe pain in multimodal pain control group and conventional pain control group, respectively. $z_{\alpha/2}$ = 1.96, α = 0.05, reliability 95%; z_{β} = 0.84, β = 0.2, power = 0.8.

According to the study of Lam[3] , p_1 was 1.79% and p_2 was 28.57%. Therefore, the minimum sample size for each group was 27. In this study, we selected 40 patients in each group.

2.5. Study process

Patients were randomized into two groups – group I, multimodal pain control group and group II, conventional pain control group (n = 40 each group). Multimodal pain regimen included intravenous paracetamol 1-2 hours before surgery, spinal anesthesia during surgery and at least two analgesic drugs after surgery. Pre-operative intravenous paracetamol was not performed in the conventional group. These two regimens were applied in the study hospital based on the WHO guideline[4] and availability of drugs in pharmacy.

Demographic data, including age, gender, comorbidities, cause of hip replacement, surgical method and operation time were collected for each patient.

On the first hospitalized day, patients were asked to assess their pain using Visual Analogue Scale (VAS, 0 = no pain, 10 = unbearable pain). On the post-operative day 1, 2, 3 (POD 1, 2, 3), the Verbal Rating Scale

(VRS) was used to measure pain level including no pain, mild pain, moderate pain and severe pain. Ambulation day was recorded as the time that patients were able to stand up without pain after surgery. Sleep disturbance nights when patient could not sleep and had to take diazepam were also documented.

Dosages of additional opioid drugs prescribed after surgeries were assessed until patients were discharged from hospital. As patients were prescribed with different opioids, dosages of opioids were converted into opioid equivalents of intravenous morphine as follow[5]

- Morphine IV:fentanyl IV = 100:1 (10 mg morphine = 100 mcg fentanyl)
- Morphine IV:tramadol IV = 1:10 (10 mg morphine = 100 mg tramadol)
- Tramadol PO:tramadol IV = 1,2:1 (120 mg tramadol PO = 100 mg tramadol IV)

Adverse events such as nausea, vomiting, stomachache, respiratory depression, urinary retention, constipation, vertigo and others were also investigated. Discharge eligibility was met when a patient is conscious, having stable vital signs and can walk with crutches or with assistance of technician in 3 continuous days.

2.6. Statistical analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) Program, version 20.0. Patient's data were presented as mean ± S.D., median (interquartile range 25-75%) or percentage. Comparison between multimodal pain control and conventional pain control group in the severe pain rates in the first 3 days after surgery, rates of sleep disturbance, and adverse event rates were assessed using Chi-square test. T-test or Mann Whitney test was used to test for significant differences in means of ambulation days, dose of opioid and length of hospital stay. The level of statistical significance was specified at $p < 0.05$.

3. RESULTS

3.1. Baseline characteristics of two study groups

Among 80 patients, 48.8% were female. Median age was 75.5 years old (61.3–83), with a proportion of those aged over 60 being 76.2%. Chronic diseases were common among patients. Hypertension (56.2%) and diabetes mellitus (23.8%) ranked the highest. Most of patients (77.5%) had at least one comorbidity, 31.3% had two and 10% had three. There were no significant differences between two study groups with respect to demographic data and comorbidities.

Most of patients suffered from femoral head fracture (78.8%) and partial hip replacement were dominant surgical method (75%). Seventy percent of patients in our study were pre-operative consulted about surgical method, analgesic regimen and expected outcome. Other important baseline characteristics were not significantly different either. The median of operative time from the skin incision to closure was 90 minutes (50–160) in group I and 90 minutes (60–225) in group II ($p = 0.119$). Median of pre-operative VAS was 5 (2 to 7) in group I and 4 (3 to 6) in group II ($p = 0.151$). Rates of pre-operative psychological consultation were 80% and 60% in group I and group II, respectively ($p = 0.051$).

The baseline characteristics of patients including demographic data, comorbidities, causes of hip replacement, surgery methods, operation time, pre-operative VAS and pre-operative patient psychological consultation were presented in table 1.

3.2. Effectiveness of multimodal regimen, compared with conventional regimen

3.2.1. Severe pain rates after surgery

The Verbal Rating Scale (VRS) was used to measure post-operative pain level. There were 3 pain levels documented comprised: mild pain, moderate pain and severe pain. Most of patients suffered from severe pain on POD 1 (57.5%). On POD 2, pain level was moderate in 63.8% and on POD 3 most of patients measured their pain level as mild (38.8%) and moderate (38.8%). Severe pain rate was lower on POD 3 but it was still considered high (22.5%).

Table 1. Baseline characteristics of the two groups

Baseline characteristic		Group I (n = 40)	Group II (n = 40)	p value
Age	(median)	75 (30–96)	77 (39–94)	0.461
	≤ 60	27.5%	20%	0.431
	> 60	72.5%	80%	
Gender	Female	47.5%	50%	0.823
	Male	52.5%	50%	
Comorbidities	Hypertension	47.5%	65.0%	0.115
	Osteoarthritis	2.5%	10%	0.359
	Diabetes mellitus	22.5%	25%	0.793
	COPD	7.5%	3.5%	0.615
	Other heart diseases	12.5%	22.5%	0.239
	Others	20%	27.5%	0.431
Cause of hip replacement	Femoral head fracture	82.5%	75.0%	0.412
	Avascular necrosis of femoral head	12.5%	17.5%	0.531
	Osteoarthritis of hip	5%	7.5%	1.000
Surgical methods	Partial replacement	75%	75%	1.000
	Total replacement	25%	25%	
Operation time	(median)	90 (50–160)	90 (60–225)	0.119
Pre-operative VAS	(median)	5 (2–7)	4 (3–6)	0.151
Pre-operative psychological consultation	Yes	80%	60%	0.051
	No	20%	40%	

*Group I: multimodal pain control group Group II: conventional pain control group
Median of age, operation time, pre-operative VAS were compared using Mann-Whitney test. Rates of osteoarthritis, COPD (comorbidities), and osteoarthritis of hip (cause of hip replacement) were compared using Fisher exact test. Chi-square test was used for others.

On POD 1, the severe pain rate of patients in group I was 32.5% compared with 82.5% of group II ($p < 0.001$). Similarly, on POD 2 and 3 patients in group I still had lower rate of severe pain compared with group II ($p \leq 0.001$) (Table 2)

3.2.2. Ambulation day

Ambulation day was recorded as the time that patients were able to stand up without pain after surgery. The average time required for ambulation was 6.33 and 9.00 days in group I and group II, respectively. This difference was statistically significant ($p = 0.001$).

3.2.3. Length of hospital stay after surgery

The mean length of hospital stay after surgery was 15 days (11-20 days) in group I and 17 days (12-26.5 days) in group II. There was no significant difference between the two groups ($p = 0.165$).

Table 2. Post-operative severe pain rates in the two study groups

	Group I (n = 40)	Group II (n = 40)	
	No. patients (Percentage)	No. patients (Percentage)	p value
POD 1			
Mild pain	2 (5)	0 (0)	p < 0.001
Moderate pain	25 (62.5)	7 (17.5)	p < 0.001
Severe pain	13 (32.5)	33 (82.5)	p < 0.001
POD 2			
Mild pain	5 (12.5)	1 (2.5)	p = 0.001
Moderate pain	31 (77.5)	20 (50)	p = 0.001
Severe pain	4 (10)	19 (47.5)	p = 0.001
POD 3			
Mild pain	23 (57.5)	8 (20)	p < 0.001
Moderate pain	15 (37.5)	16 (40)	p < 0.001
Severe pain	2 (5)	16 (40)	p < 0.001

*Group I: multimodal pain control group Group II: conventional pain control group
Percentages of mild pain (POD 1, POD 2) were compared using Fisher exact test. Chi-square test was used to compare other percentages.

3.2.4. Sleep disturbance

Eighteen point eight percent of patients in our study had sleep disturbance at least one time after surgery. The sleep disturbance rate of group I was 5% compared with 32.5% of group II (p = 0.003).

3.2.5. Opioid consumption

In this study, patients were prescribed intravenous opioid as fentanyl or tramadol in the first 3 days after surgery. Opioid dosages were adjusted to individual pain level. On the following days, if patients still suffered from severe pain, Ultracet PO would have been added (Ultracet: 37.5 mg tramadol + 325 mg paracetamol). In order for comparison, dosages of opioid were converted into opioid equivalents of intravenous morphine. Total opioid consumption of group I during entire hospital stay was 23.1 mg (12.5-30 mg) and that of group II was 32.5 mg (30-40 mg) (p = 0.023).

3.2.6. Adverse event rates

The rates of adverse drug events of the two groups were shown in table 3.

4. DISCUSSION

Most of patients in our study were aged above 60 (76.2%). Median age of patients in our study was higher than those involved in Peters et al.[6] study (57 years old) and Lee et al.[7] study (53 years old). The explanation is that most of patients in Thong Nhat hospital were veterans. It also explains why there was a higher proportion of male in our study as compared to Chammout et al.[8]

Femoral head fracture was the most common among hip replacement patients (78.8%). This could be blamed for their advancing ages which are closely related to lower bone density. Consequently, partial hip replacement was dominant surgical method (75%). There were no significant differences between two groups with respect to causes of hip replacement and surgery methods.

Table 3. Adverse drug events of two groups

ADE	Group I (n = 40)	Group II (n = 40)	p value
	No. patients (%)	No. patients (%)	
Nausea and vomiting	3 (7.5)	2 (5)	1.000
Stomachache	0 (0)	3 (7.5)	0.241
Respiratory depression	2 (5)	3 (7.5)	1.000
Urinary retention	6 (15)	8 (20)	0.556
Constipation	1 (2.5)	6 (15)	0.108
Vertigo	1 (2.5)	3 (7.5)	0.615

*Group I: multimodal pain control group Group II: conventional pain control group
Percentage of patients who suffered from urinary retention, constipation was compared using Chi-square test. Fisher exact test test was used for comparing other percentages.

About operative time, according to Gaglisese L.[9], the longer operative time was, the more painful experience was expected. However, the difference between two groups was not statistically significant (p = 0.119).

Median of pre-operative VAS was 4 (3 to 5) and most of patients (61.3%) suffering from moderate pain on the first day of hospitalized. Pre-operative pain can be a confounding variable because patients tend to compare their post-operative pain with their own pain perception before. However, there were no significant differences between two groups with respect to pre-operative VAS score.

Seventy percent of patients in our study were pre-operative consulted about surgical method, analgesic regimen and expected outcome. Psychological factors such as past pain experience and pain level expectation may impact on patients by changing their pain perceptions. Pre-operative consultation brings patients relief and it results in a better pain control provided that adequate information could give patients realistic expectations of the care (pain relief not pain free). Mamie et al.[10] reported that there was a correlation between pain expectation and post-operative severe pain rates. This indicates that a pre-operative discussion with patients can be helpful about an effective post-operative pain management. However, no significant difference between two groups were documented (p = 0.051).

Totally, there were no significant differences between two study groups with respect to demographic data, comorbidities, causes of hip replacement, surgery methods, operation time, pre-operative VAS and pre-operative patient psychological consultation (p > 0.05).

In this study, the multimodal therapy was shown to significantly reduce pain level from the first day after surgery to the 3th post-operative day. This therapy was also found to be quite reliable as just 5% of patients had severe pain on POD 3. In contrast, patients in group II had significantly more pain with 40% patients suffering from severe pain (p < 0.001). The better pain control of group I can be explained by the prevention of pain stimuli central sensitization because of the use of pre-emptive analgesia (paracetamol IV 1-2 hours before surgery). Similarly to this present study, Parvataneni et al.[2] concluded that patients in multimodal pain control group suffered less pain than those of conventional group (p = 0.0067). In 2006, Peters et al.[6] had widen the inclusion of patients with hip replacement and knee replacement, remained the same conclusion of positive impact of multimodal regimen. Other studies such as those of Helb et al.[11] Lee et al.[7] had the same outcome. This indicated that multimodal pain management had produced a good pain relief in the first 3 days after surgery.

However, according to Burn et al.[12], various factors such as age, gender and pain relief expectation can affect the awareness of pain after surgery. Therefore, in this study, we used multiple logistic regression model to consider those effects on severe pain rates of POD 1, 2, 3. However, either age, gender or pain relief expectation has no significant effect on POD 1, 2, 3 severe pain rates ($p > 0.05$). Meanwhile, it is dependent on pain management protocol (multimodal pain management protocol) ($p < 0.001$, $p = 0.002$ and $p = 0.002$ on POD 1, 2 and 3, respectively).

As pain is a unique experience for each individual, responses to post-operative pain management may be vary. Therefore, in order to evaluate the effectiveness of a pain management protocol, other clinical outcomes such as functional recovery, opioid consumption or complications should be taken into account.

Patients with lower pain level will get this milestone earlier. Since patients could stand up from bed, they will be able to access to physiotherapy and gained faster recovery to normal daily activities. Earlier ambulation also brings patient satisfaction. On the contrary, delayed ambulation leads to other unwanted complications such as paralytic ileus, venous thromboembolism and pneumonia. The result showed that patients with multimodal therapy recovered faster than those in conventional therapy group ($p = 0.001$).

A study conducted in 2009 by Lee et al.[7] shown similar outcome of multimodal analgesic group, average time required for patients to be able to perform straight leg raising exercises without pain and ambulation with the aid of crutches was 2.8 days in multimodal group and 5.3 days in conventional group ($p < 0.001$). In comparison to this present study, patients in Lee et al.[7] study needed less time to recover because of their younger age. Similarly, Lam[3] showed that multimodal pain control group started physiotherapy after surgery 1.54 ± 0.76 days while the conventional one took 3.39 ± 0.68 days ($p < 0.001$). Patients in Lam[3] study recovered faster as the fact that they were used epidural anesthesia along with spinal anesthesia during operation period.

In this study, there was no significant difference in the length of hospital stay after surgery between the two groups ($p = 0.165$). This result is consented with Lee et al.[7] and Busch et al.[13] However, in a study of Helb et al.[11] , patients who had been managed with the multimodal regimen were discharged from the hospital significantly earlier than those of the conventional pain control group (2.8 days compared with 5.0 days; $p < 0.01$). Peters et al.[6] (2006) and Parvataneni et al.[2] (2007) also consented with Helb et al.[11] when concluded a reduction of hospital stay in multimodal pain control group.

The sleep disturbance rate of group I was significantly lower compared with group II ($p = 0.003$). Lam[3] who used the Brief Pain Inventory (BPI) score to assess the impact of pain on sleep, had come to the same conclusion. Stress and painful experiences are main reasons of sleep disturbance after surgery. Sleep disturbance brings dissatisfaction and slows down rehabilitation process. A comprehensive pain management should have relieved pain and produced patient satisfaction including sleeping quality. Sound sleeping may lead to rapid recovery and this can be inferred that multimodal regimen have had positive impact on patient emotion as well as their recovery.

The result showed that, patients in group I used significantly less opioid than group II ($p = 0.023$). Study of Duellman et al.[14] had similar result with the total morphine consumption of multimodal regimen group (6.4 mg) significantly lower than those of conventional one (17.6 mg) ($p < 0.05$). The morphine consumption in multimodal protocol group of Peters et al.[6] study (2006) was 49 mg, significantly lower than 91 mg for the conventional group ($p < 0.001$). The results were also repeated in Helb et al.[11] study.

This indicates that multimodal regimen have reduced opioid consumption on hip replacement patients. Traditionally, the administration of intravenous opioids has been playing a main role for post-operative pain management. However, intravenous opioids are commonly associated with sedation and other adverse side effects such as nausea, vomiting, gastrointestinal

ileus and pruritus. Meanwhile, patients undergoing hip replacement are elderly people and are more sensitive to those unwanted effects. Therefore, that multimodal pain therapy has reduced opioid consumption is meaningful for hip replacement patients.

Urinary retention was the most common among other adverse events (17.5%). Constipation made up 8.8%, ranked second. High rate of urinary retention was caused by painful experience and orbicularis spasm. It was also a common ADE of spinal anesthesia. Constipation was a result of opioid side effect on gastrovermiculation, severe pain, anxiety and poor diet.

Nausea and vomiting, respiratory depression occurred in 6.3% patients. This rate was lower than that of Lam[3] (18.8%) and Hebl et al.[11] (32%).

Vertigo and stomachache had lowest rates (5% patients had vertigo and 3.8% suffered from stomachache). Vertigo is a common ADE of gabapentin though it passes by quickly and sometimes it is not recorded. Post-operative stress and NSAIDs may responsible for stomachache. However, stomachache had low rate because of the protection of omeprazole 20 mg twice a day for those who potentially develop into GI bleeding.

There was no difference between the two groups in the proportion of patients who experienced nausea, vomiting, stomachache, respiratory depression, urinary retention, constipation or vertigo.

Contrary to our findings, the rates of patients who had nausea, vomiting, stomachache, respiratory depression were significantly lower in multimodal pain control group, according to a study conducted in another Vietnamese hospital[3]. Helb et al.[11] concluded that significantly fewer patients in the multimodal regimen group experienced post-operative urinary retention than that of the control group ($p < 0.001$). The differences may be due to the small sample size of our study while adverse drug events are rare.

In conclusion, this study demonstrated better pain control for group I. Patients in multimodal pain control group had significantly lower rate of severe pain in the first 3 days after surgery ($p \leq 0.001$), significantly lower rate of sleep disturbance ($p = 0.003$) satisfaction including sleeping quality. Sound sleeping may lead to rapid recovery and this can be inferred that multimodal regimen have had positive impact on patient emotion as well as their recovery, significantly earlier ambulation ($p = 0.001$), and significantly lower dose of opioid used ($p = 0.023$), compared with those in group II. However, there were no significant differences in hospital stay and adverse event rates ($p > 0.05$).

Despite these encouraging findings, the retrospective nature shows its weakness when assessing pain qualitatively instead of quantitatively. A prospective study using validated patients assessment tools may have given a more accurate assessment of the differences noted here.

5. CONCLUSION

The use of a variety of pharmacological agents with different mechanisms results in superior pain relief. In addition, use of preemptive analgesia paracetamol IV 1-2 h before incision shows positive impact on pain control, earlier functional recovery as well as reduced opioid consumption. The results of this study demonstrate a good pain relief and functional recovery after hip replacement with the use of the multimodal protocol described. Therefore, it can be substituted for conventional pain control regimen.

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