Original Article

การสำรวจผลของการบรรเทาอาการปวดในผู้ป่วยมะเร็งตามแนวปฏิบัติขององค์การอนามัยโลก

Exploration the Results of Cancer Pain Management Following Implemation of World Health Organization (WHO) Pain Guideline

สุภัสร์ สุบงกช[*1], ศุกัญญา ควรนิคม[2], นุจรี ประทีปะวณิช จอห์นส[1], เอื้อมแข สุขประเสริฐ[3]

Suphat Subongkot[*1], Sugunya Khounnikhom[2], Nutjaree Pratheepawanit Johns[1], Aunkhae Sookprasert[3]

[1] คณะเภสัชศาสตร์ มหาวิทยาลัยขอนแก่น อ.เมือง จ.ขอนแก่น 40002

Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen 40002

[2] โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ อ.คลองหลวง จ.ปทุมธานี 12120

Thammasat University Hospital, Klongnung Klongluang, Pathumthan 12120

[3] คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น อ.เมือง จ.ขอนแก่น 40002

Faculty of Medicine, Khon Kaen University, Khon Kaen 40002

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Abstract

Background: Pain is among the most common symptoms encountered in cancer patients and remains the first priority of care.

Methods: This cross sectional study aimed to explore a result of pain management at Srinagarind Hospital, Khon Kaen University following the implementation of World Health Organization (WHO) pain guideline. Cancer pain patients were categorized based on prior analgesic exposure into two groups; Naive group, and Routine group. Treatments were defined according to WHO as 1) drug treatment relevant to pain severity, 2) analgesics being prescribed as around-the-clock and 3) analgesics used for break-through pain for patients receiving strong opioids.

Results: From Dec 2005 to Jul 2006, 261 patients were enrolled. 93.1% (n=243) were in advanced stages and 88.5% (n=231) were in moderate to severe pain.

In Naive group (n=159), 32.7% (n=52) of patients were given analgesics following the WHO on both days 1 and day 3 of admission; 3.8 %(n=6) of patients followed WHO only on day 1; 23.3 %(n=37) of patients followed WHO only on day 3 whereas 40.2% (n=64) of patients did not follow WHO on both days. A decreased pain score was greater (2.61, SD±1.5) in a group following the WHO both days on day 1 and a decreased pain score was much improved (3.9, SD±1.8) as continuing to follow WHO on day 3 ($p < 0.0001$) compared to those not following WHO on both days.

* ผู้เขียนที่สามารถติดต่อได้ : สุภัสร์ สุบงกช คณะเภสัชศาสตร์ มหาวิทยาลัยขอนแก่น โทรศัพท์ 0-4320-2378 โทรสาร 0-4320-2379

email : subsup2@kku.ac.th

In Routine group (n=102), 31.4% (n=32) of patients were given analgesics following the WHO guideline on both day 1 and day 3 of admission. 5.9 %(n=6) of patients followed WHO only on day 1; 27.5 %(n=28) of patients followed WHO only on day 3 while 35.3% (n=36) of patients did not follow WHO on both days. A decreased pain score was statistically significant greater (2.6, SD±1.8) in a routine group following the WHO both days on day 1 ($p < 0.0001$). Furthermore, a decreased pain score was even greater (3.9, SD±2.3) in the routine group continuing to follow WHO on day 3 compared to those not following WHO on both day 1 and day 3 of admission. The most common of adverse effects related to analgesics was constipation.

Conclusions: The results demonstrated that patients who received pain management following the WHO guideline reported significantly lower pain intensity than those not following the WHO regardless the history of analgesics exposure.

Keyword: Cancer, Pain, Analgesics

บทคัดย่อ

ที่มา: มะเร็งเป็นโรคที่มีผลกระทบต่อคุณภาพชีวิตของผู้ป่วยเนื่องจากอาการแทรกซ้อนและพบว่าผู้ป่วยมะเร็งระยะลุกลามมักจะมีอาการปวด ดังนั้นอาการปวดจึงเป็นปัญหาสำคัญลำดับต้นในการบริบาลผู้ป่วย

วิธีวิจัย: การศึกษานี้เป็นการศึกษาแบบเวลาใดเวลาหนึ่งแบบภาคตัดขวาง (Cross-section study) มีวัตถุประสงค์เพื่อสำรวจผลของการรักษาอาการปวดของผู้ป่วยมะเร็งในโรงพยาบาลศรีนครินทร์ มหาวิทยาลัยขอนแก่นตามแนวปฏิบัติขององค์การอนามัยโลก (World Health Organization: WHO) การศึกษานี้แบ่งผู้ป่วยเป็น 2 กลุ่ม ได้แก่ กลุ่มที่ไม่เคยได้รับยา (naïve group) และกลุ่มที่ได้รับยาเป็นประจำ (routine group) ผู้ป่วยที่ได้รับการรักษาตามแนวปฏิบัติขององค์การอนามัยโลก จะต้องมีเกณฑ์ดังนี้คือ 1. ได้รับยาที่สัมพันธ์กับระดับขั้นขององค์การอนามัยโลก (WHO three-step ladder guidelines) 2. ได้รับยาแบบตลอดช่วงเวลา (Around-the-clock) 3. ได้รับยารักษาอาการปวดเฉียบพลัน (Break-through pain analgesic)

ผลการศึกษา: ในระหว่างเดือนธันวาคม 2548 ถึงกรกฎาคม 2549 มีผู้ป่วยมะเร็งที่เข้าเกณฑ์การศึกษาจำนวน 261 คน ผู้ป่วยส่วนใหญ่ร้อยละ 93.1 (243 คน) มีภาวะโรคมะเร็งระยะลุกลาม และร้อยละ 88.5 (231 คน) จากผู้ป่วยทั้งหมดมีอาการปวดระดับปานกลางถึงปวดรุนแรง

ผลการสำรวจในกลุ่มผู้ป่วยที่ไม่เคยใช้ยาบรรเทาอาการปวดมาก่อน (naïve group) 159 คน พบว่ามีผู้ป่วยที่ได้รับยาบรรเทาอาการปวดตาม WHO ทั้งวันที่ 1 และวันที่ 3 จำนวน 52 คน (32.7%) ผู้ป่วยที่ได้รับยาบรรเทาอาการปวดตาม WHO เฉพาะวันที่ 1 หรือวันที่ 3 จำนวน 6 คน (3.8%) และ 37 คน (23.3%) ตามลำดับ ในขณะที่มีผู้ป่วยที่ไม่ได้รับยาตาม WHO ทั้งวันที่ 1และวันที่ 3 จำนวน 64 คน (40.2%) ผลการศึกษาในด้านการรักษาอาการปวดในวันแรกพบว่ากลุ่มผู้ป่วยที่ได้รับยาตาม WHO ทั้งสองวันจำนวน 52 คน มีระดับของอาการปวดที่ลดลง 2.6 (SD±1.5) ตาม NRS และระดับอาการปวดจะลดลง 3.9 (SD±1.8) อย่างต่อเนื่อง ในวันที่ 3 เมื่อเปรียบเทียบกับกลุ่มผู้ป่วยที่ไม่ได้รับยาตาม WHO ทั้งสองวัน โดยระดับอาการปวดที่ลดลงนั้นมีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (p-value < 0.0001)

ผลการสำรวจในกลุ่มผู้ป่วยที่ใช้ยาเป็นประจำ (routine group) จำนวนทั้งหมด 102 คน พบว่าผู้ป่วยที่ได้รับยาบรรเทาอาการปวดตาม WHO ทั้งวันที่ 1 และวันที่ 3 มีจำนวน 32 คน (31.4%) มีผู้ป่วยที่ได้รับยาบรรเทาอาการปวดตาม WHO เฉพาะวันที่ 1 หรือวันที่ 3 จำนวน 6 คน (5.9%) และ 28 คน (27.5%) ตามลำดับ ในขณะที่ผู้ป่วยที่ไม่ได้รับยาตาม WHO ทั้งสองวันมีจำนวน 36 คน (35.3%) ในวันแรกของการรักษาพบว่ากลุ่มผู้ป่วยที่ได้รับยาตาม WHO ทั้งสองวัน มีระดับอาการปวดลดลง 2.6 (SD±1.8) อย่างมีนัยสำคัญทางสถิติ (p-value < 0.0001) เมื่อเปรียบเทียบกับผู้ที่

ไม่ได้รับยาตาม WHO และมีระดับอาการปวดที่ลดลง(3.95 (SD±1.8) อย่างต่อเนื่องในวันที่ 3 เมื่อเปรียบเทียบกับกลุ่มผู้ป่วยที่ไม่ได้รับยาตาม WHO ทั้งในวันที่ 1 และวันที่ 3 ภายหลังจากที่เข้ารับการรักษาในโรงพยาบาล สำหรับอาการข้างเคียงที่สำคัญของยาบรรเทาปวด คือ อาการท้องผูก

บทสรุป: การศึกษาครั้งนี้พบว่าผู้ป่วยมะเร็งที่ได้รับยาบรรเทาอาการปวดอย่างเหมาะสมตามแนวทางขององค์การอนามัยโลกจะสามารถควบคุมระดับความปวดได้อย่างมีประสิทธิภาพมากกว่าผู้ป่วยที่ไม่ได้รับยาตามมาตรฐานแนวปฏิบัติทั้งในกลุ่มผู้ป่วยที่เคยและไม่เคยใช้ยาบรรเทาปวดมาก่อน

คำสำคัญ: ความปวด อาการปวด ยาบรรเทาปวดโรคมะเร็ง

Introduction

Cancer is one of the major problems in global health care. The incidence of cancer has been increasing around the world for the past decades (WHO, 2006). In the year 2005, cancer was the second leading cause of death and accounting for nearly 7 million deaths each year globally (WHO, 2006). In the year 2006, more than 24.6 million people were living with cancer, and by 2020 it is projected that there will be approximately 16 million newly diagnosed cancer cases and 10 million people will die with cancer (Steward and Kleihues, 2003; WHO, 2006).

Despite significant advancement in treatments over the past 5 years, cancer remains the primary cause of death in Thailand (Sriplung et al., 2003). Cancer also represents the top rank of all disease related deaths which accounted for 50,662 patients in year 2005 (Attasara, 2005). These numbers of death caused by cancer were higher than those of the people dying from accidents and poisoning. Cancer has become a major public health problem in Thailand with a rate of 165 to 200 per 100,000 populations in the year 2005 (Sriplung et al., 2003).

Throughout the clinical course of the disease, cancer patients usually suffer from a variety of symptoms, such as pain, dyspnea and fatigue. Pain is one of the most frequent and deleterious symptoms observed in approximately 30% of cancer patients receiving cancer therapy and in approximately 70% of patients with advanced cancers (Ger, 1998; Higginson, 1997). At diagnosis one third of these cancer patients will experience some pain. This proportion of pain will increase up to 90% in patients with advanced stages of diseases (Landis et al., 1999). Etiologies of pain in cancer patients are mostly (40-92%) caused by the disease itself which involve the invasion of soft tissues, visceral organ, bone and nervous system. Other causes are related to cancer treatment (5-20%) such as surgical incision pain, mucositis and concomitant medical conditions (8-22%) such as arthritis (Grond et al., 1996). The severity of pain in cancer patients may be related to gender, age, characteristics of pain, location of pain, number of pain sites and past pain experience all of which affect the pain behavior in many different ways. Furthermore, unrelieved pain has a negative impact on the quality of the patient's life including physical, psychological, social and spiritual aspects (Breitbart, 1994).

There are a variety of pain management methods for relieving cancer pain. In 1986, the World Health Organization (WHO) published guidelines for cancer pain management based on the three-step analgesic ladder. These steps comprise of a sequential approach according to the individual pain intensity. The first analgesic ladder (Step I) includes the use of non-steroidal anti-inflammatory drugs (NSAIDs) and other non-opioids drug for mild to moderate pain. Opioids should be added to the NSAIDs if pain persists or increases or

if pain is still moderate to severe intensity. Typically, combination opioids will be used for moderate pain constituted the second analgesic ladder (Step II). If pain continues unrelieved or is severe in intensity, higher potency opioids should be instituted in the third analgesic ladder (Step III). The important concepts in the WHO approach include the preferred use of drugs by mouth, by the clock and by the ladder. Individual flexibility and attention to details are strongly recommended. Health care providers should also take into account the individual response to analgesics as well as the possible occurrence of adverse effects and subsequently treat the patient appropriately. Medications should be administered by the least invasive and the most convenient route available to provide the patient with adequate analgesia (Foley, 1985). In the presence of persistent pain, medication should be administered around-the-clock. Attention should be paid to the individual response of patients, and a continuous pain assessment is recommended. Regular monitoring for possible adverse effects, as well as managing these effects, is mandatory (Foley, 1985).

Since 1986, the WHO cancer pain relief guideline was first published and validated, the impact has been wide-reaching, and there are many reports of enhanced pain alleviation in cancer patients however there were patients who were left untreated (Zech, 1995). Undertreatment of cancer pain contributes to an internationally supportive care problem due to the fact that 50-80% of cancer patients still suffered from uncontrolled pain (Stjernsward et al., 1996). The reasons for under pain-treatment include poor pain assessment by clinicians as well as the clinician's perception of less importance for pain management compared with other therapies; patient's reluctancy to report pain, or to take opioid-analgesics; and physicians'reluctancy to prescribe opioids (Hammack and Loprinzi, 1994). Bral et al. reported in 1998 that 42% of outpatients with cancer in United States did not receive enough pain management and 14% of cancer patients died without pain proper pain controll at the end of life or hospice facility (Bral, 1998). A study performed by Vatanasapt et al. in 1992 at Srinagarind Hospital reported that approximately 30% of cancer patients who experiencing pain did not receive any pain medication during their hospital courses (Vatanasapt et al., 1992). In addition, those who did receive pain medication should have had a better pain control. Recently, the pattern of treatment in cancer pain might be improving due to the increase of pain management knowledge, availability of analgesic types and dosage forms and also the globally available WHO pain management guideline. The results of several studies demonstrated that pain intensity decreased within the first day of pain management initiated (Cleeland, 1996). Additionally, the study performed by Frame et al., demonstrated that the pain score was continuously decreased on the third day of implementing the pain guideline (Frame, 2000). It would be of interest to investigate cancer pain management after three days of pain management in Srinagarind Hospital. This study hypothesized that the pain score of cancer patients who received pain management following the WHO guideline would be more tolerable than those who did not receive pain management following the WHO guideline.

Objective

This study is aimed to explore the result of cancer pain management at Srinagarind Hospital, Khon Kaen University

Materials and Methods

The study was a cross-sectional design conducted at Srinagarind Hospital, Khon Kaen University, Thailand. Data were collected by using an interview method at baseline before the initiation

of pain management, and at the first day and the third day after the treatment during December 2005 to July 2006. Patients were included if they were between 15 to 70 years old; admitted to the studied hospital with cancer pain; received cancer pain management in hospital not less than three consecutive days; could understand and communicate in Thai. Patients were excluded if they refused to participate in the study; had an operation less than one month prior to the study; could not follow the instructions of the questionnaire and unavailable to be contacted for the follow-up. The pain assessment tools in this study consisted of a numerical rating scale (NRS), analgesics utilization diary, and questionnaires on patient's daily life activities before and after admission. The study procedures were displayed in Figure 1. For comparing the magnitude of pain scores decreased following WHO pain management guideline, all eligible cancer patients with pain were categorized based on history of analgesics exposure into two groups; group I, the naïve group defined as patients who had never been exposed to analgesics or did not take analgesics routinely; group II, the routine group defined as patients who took analgesic routinely a week prior admission. These groups were subcategorized into those who followed WHO pain management guideline described as 1) Drug treatment being used relevant to the pain severity based on the WHO three-step ladder 2) Drug treatment being prescribed around-the-clock (ATC) for pain management and 3) Drug treatment being given for break-through pain management in patients prescribed strong opioids, and those who did not follow WHO and were observed on day one and day three of admissions. The Microsoft Access Database 2000 software was used to store the collected data and SPSS Version 11.5 Statistical Software Sackage for Windows was used for data analysis. The Kolmogorov-Smirnov test was used to determine normality of the data. Parametric statistical analysis was used for normally distributed data, and non-parametric statistical analysis was used for non-normally distributed data. P-values of less than 0.05 were considered statistically significant.

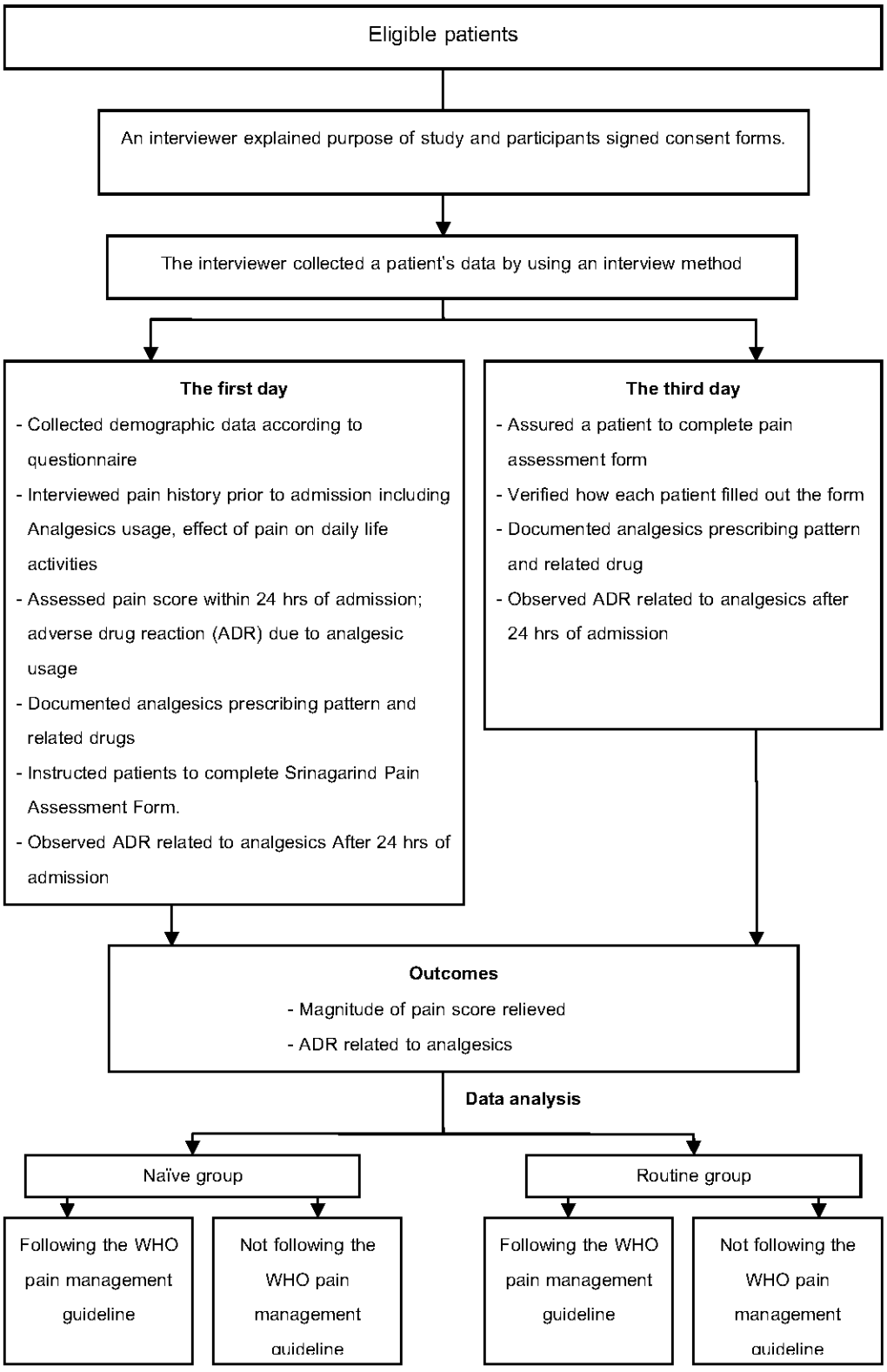

Figure 1 Study procedure flow chart.

Results

Patients' characteristics

Between December 2005 to July 2006, 278 cancer pain patients recruited into our study. Nevertheless, four patients with head and neck cancer dropped out because of disease progression. Six patients were excluded due to operation and two patients were lost for the follow-up. In addition, five patients who received analgesics on the first day of admission with pain free were excluded. At the end of the study period, 261 eligible cancer pain patients were categorized into two groups.

Of the 261 evaluated patients, 60.9% patients (n=159) were classified as naïve group (group I), and 39.1% patients (n=102) were classified as routine group (group II). The results of pain management in each group are described in Figure 2.

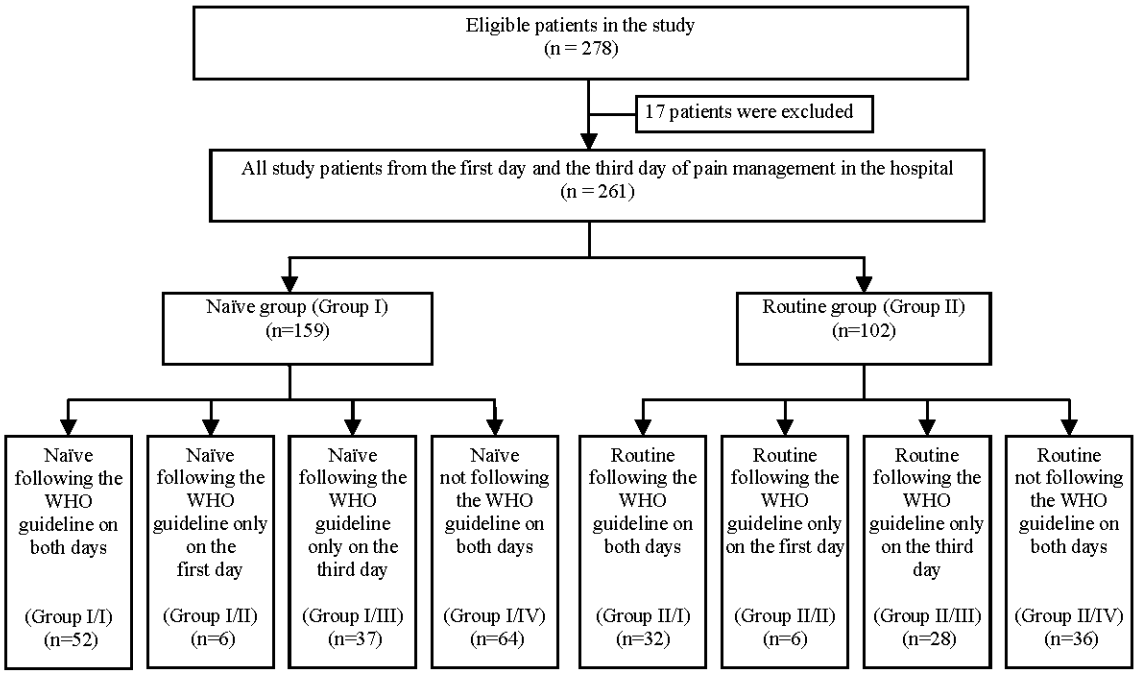

Figure 2 Flow chart of patient's group classification.

Approximately two thirds (63.6%, n=166) of the patients in this study had more than one type of pain as shown in Table 1. An average pain score at one week prior to admission was 6.0 (SD±2.6). An average pain severity measured by numerical rating scale (NRS) within 24 hours prior to analgesics treatment ranged between 6.6 (SD±2.5) for maximum pain, and 3.6 (SD±2.8) for least pain, whereas an average current pain score at the time of measurement was 4.3 (SD±2.4). Most patients described a pain score of 5.7 (SD±1.7) as tolerable. Common medications for pain relief prior to admission were NSAIDs (27.6%, n=72), weak opioids (36.0%, n=94) and strong opioids (13.4%, n=35), respectively. In contrast, there were 22.6% of the patients (n=59) who had never used either medications or alternative therapies for relieving pain prior to admission.

Table 1 Characteristics of pain and analgesic treatment of 261 patients on the first day of admission.

Characteristics		n	%
Type of pain			
Somatic pain		59	22.6
Visceral pain		23	8.8
Neuropathic pain		13	5.0
Somatic + visceral pain		54	20.7
Somatic + neuropathic pain		75	28.7
Visceral + neuropathic pain		11	4.2
Somatic + visceral + neropathic pain		26	10.0
Number of pain locations			
1		101	38.7
2		84	32.2
3		52	19.9
More than 3		24	9.2
Level of pain intensity within 24 hours prior to analgesic treatment[a]			
1		30	11.5
2		106	40.6
3		125	47.9
Pain scores within 24 hours prior analgesic treatment (total score = 10)			
Maximum pain (Mean ± SD)[b]	6.6 ± 2.5		
Least pain (Mean ± SD)[c]	3.6 ± 2.8		
Current pain (Mean ± SD)[d]	4.3 ± 2.4		
Tolerable pain (Mean ± SD)[e]	5.7 ± 1.7		
Pain scores one week prior admission[f]	6.0 ± 2.6		
Analgesics used at one week prior to admission			
Non-used		59	22.6
NSAIDs[g]		72	27.6
Weak opioids		94	36.0
Strong opioids		35	13.4
Adjuvants		1	0.4

[a] The maximum pain intensity measured within 24 hours prior to admission. Measurement by numerical rating scale (NRS), scales were classified as 1-3 = mild pain, 4-6 = moderate pain and 7-10 = severe pain.

[b] The maximum pain intensity measured within 24 hours prior to admission.

[c] The least pain intensity measured within 24 hours prior to admission.

[d] The pain intensity measured during meet physician at the first time of the current admission.

[e] The pain intensity that patient could be acceptable without analgesics or no need for more analgesics.

[f] The average pain score measured at one week prior to admission.

[g] Non steroidal anti-inflammatory drugs.

Comparison of pain management in the naïve patients completely following WHO guideline and in the naïve patients not following WHO guideline

Of the 159 patients in the naïve group, 32.7% of patients (n=52) were classified as the naïve completely following the WHO guideline on both days (Group I/I) and 40.2% of patients (n=64) were classified as the naïve not completely following both days group (Group I/IV). In addition, 27% of patients (n=43) appeared to partially follow WHO including 3.8% of patients (n=6) following WHO only on day 1 (Group I/II) and 23.3% of patients (n=37) following WHO only on day 3 (Group I/III) as described in Figure 2.

Among the 52 patients in Group I/I, the maximum pain scores on average reported in the numerical rating scale (NRS) prior to and after receiving a medication for pain management were 5.3 (SD±1.9) and 2.7 (SD±1.1), respectively. The mean difference of the pain score compared at time prior to and after first day of admission was decreased by 2.6 (SD±1.5). Most patients (73.1%, n=38) were in moderate pain, 11.5% of patients (n=6) were in mild pain and 15.4% of patients (n=8) were in severe pain. The majority of patients (73.1%) were prescribed pain medications in Step II (weak opioids). All the patients in this group also received around-the-clock analgesics regimen and strong opioids for break-through pain regimen recommended by WHO as appeared on Table 2.

On the third day of admission, the maximum pain scores on average after receiving pain management was 1.4 (SD±0.9). A mean difference of pain score compared at time prior to admission on the first day and after receiving pain management on the third day was decreased by 3.9 (SD±1.8). Almost all of the patients (98.1%, n=51) were shifted to mild pain and only 1.9% of patients (n=1) were still in moderate pain. The majority of pain management assigned was in Step II (weak opioids) reported to be 78.8% (n=41). All patients in this group also received around-the-clock analgesics and medication for break-through pain regimen. There was a statistically significant difference in the decrease of pain scores (-3.9, SD±1.8; p-value < 0.0001) on the third day of pain management as compared to the decrease of pain scores (-2.6, SD±1.5) on the first day of admission. These decreased pain scores may have been of clinically significance if the pain severity scale based on WHO three step ladders was shifted to the less severity level.

Table 2 Summary of pain management in the naïve group (Group I/I) who followed the WHO guideline on both days; n = 52.

Variables	Day of follow-up		p-value[g]
	First Day	Third day	
Average of maximum pain after pain management initiated[a], mean ±SD (Median ± IQR)[b]	2.7 ± 1.1 (3 ± 2)	1.4 ± 0.9 (1.5 ± 1)	0.0001
Type of pain severity			
Mild, n (%)	6 (11.5%)	51 (98.1%)	-
Moderate, n (%)	38 (73.1%)	1 (1.9%)	-
Severe, n (%)	8 (15.4%)	-	-
Type of pain management			
Step I (non-opioids)	6 (11.5%)	2 (3.8%)	-
Step II (weak opioids)	38 (73.1%)	41 (78.8%)	-
Step III (strong opioids)	8 (15.4%)	9 (17.3%)	-
Interval of pain management administration			
Around-the-clock	52 (100%)	52 (100%)	-
As-needed	-	-	-
Use of break-through pain analgesic for moderate pain	7 (18.4%)[d]	7 (17.0%)[d]	-
Use of break-through pain analgesic for severe pain	8 (100%)[e]	9 (100%)[e]	-
Difference of pain score compared with score prior to the first day[c] and after pain management, mean ±SD	- 2.6 ± 1.5	- 3.9 ± 1.8[f]	0.0001
Rang of difference of pain score	-3 to -2	-4.8 to -3	-

[a] For the first day, average of maximum pain score in every period from patients' self report
For the third day, average of maximum pain score in four periods on the third day of follow-up.

[b] Because patient's pain scores were not normal distributed.

[c] Average of maximum pain score 24 hours before pain management initiated on the first day, mean ±SD (Median ± IQR); 5.3 ± 1.9 (5 ± 4).

[d] Calculated from proportion of patients who received weak opioids and also received break-through analgesic for moderate pain.

[e] Calculated from proportion of patients who received strong opioids and also received break-through analgesic for severe pain.

[f] Clinical significance (> 3 points): Clinical significance is observed after pain score reduced greater than 3 points (Thienthong et al., 2006).

[g] Wilcoxon Signed Ranks test p-value.

Of the 64 patients in Group I/IV, the maximum pain scores on average per NRS scale prior to and after first day of admission were 6.6 (SD±2.3) and 5.5 (SD±2.4), respectively. These baseline scores appeared to be higher than those reported in Group I/I. The mean difference of pain score compared at time prior to and after first day of admission was reduced by 1.2 (SD±1.2). More than half of the patients (50.0%, n=32) were in severe pain as compared to mild to moderate pain reported in Group I/I. The majority of pain managements assigned were in Step I (non-opioids) up to 64.1% (n=41) instead of being prescribed based on appropriate pain severity scale. There were 28.8% of patients in this group receiving around-the-clock analgesics regimen, and only 8.3% of patients had received strong opioids for break-through pain as demonstrated in Table 3.

On the third day of admission, the maximum pain scores on average after receiving pain medications was 4.4 (SD±2.3) which appeared to be greater than those reported in Group I/I (1.4 (SD±0.9)). A mean difference of pain score compared at time prior to admission and after receiving pain management on the third day was reduced by 2.2 (SD±0.8) while there was a decreased pain score of 3.9 (SD±1.8) reported in Group I/I. The majority of patients (46.9%, n=30) were in moderate pain compared to mild pain reported in those of Group I/I. The majority of pain managements assigned were in Step I (non-opioids) up to 59.4% (n=38) though majority of patients were in moderate to severe pain intensity. There were 32.8% of patients in this group receiving around-the-clock analgesics regimen and 7.6% of patients receiving strong opioids for break-through pain as compared to all patients in Group I/I receiving around-the-clock analgesics and medication for break-through pain per WHO recommendation. There was a statistically significant difference in the decrease of pain scores from based line (-2.2, SD±0.8; p-value < 0.0001) on the third day of pain management as compared to the decrease of pain scores (-1.2, SD±1.2) on the first day of admission. Nonetheless, the magnitude of pain score reduction observed in Group I/IV seemed to be less clinically significant. The summary of pain management comparison in the naïve patients completely following WHO guideline (Group I/I) and in the naïve patients not following WHO guideline (Group I/IV) was illustrated in Table 4.

Table 3 Summary of pain management in the naïve group (Group I/IV) who did not followed the WHO guideline on both days; n= 64.

Variables	Day of follow-up		p-value[f]
	First Day	Third day	
Average of maximum pain after pain management initiated[a], mean ±SD (Median ± IQR)[b]	5.5 ± 2.4 (5.2±4)	4.4 ± 2.3 (4.7±2.6)	0.0001
Type of pain severity			
Mild, n (%)	9 (14.1%)	23 (35.9%)	-
Moderate, n (%)	23 (35.9%)	30 (46.9%)	-
Severe, n (%)	32 (50.0%)	11 (17.2%)	-
Type of pain management			
Step I (non-opioids)	41 (64.1%)	38 (59.4%)	-
Step II (weak opioids)	11 (17.2%)	13 (20.3%)	-
Step III (strong opioids)	12 (18.8%)	13 (20.3%)	-
Interval of pain management administration			
Around-the-clock	18 (28.1%)[d]	21 (32.8%)[d]	-
As-needed	46 (71.9%)[e]	43 (67.2%)[e]	-
Use of break-through pain analgesic for moderate pain	-	-	-
Use of break-through pain analgesic for severe pain	1 (8.3%)	1 (7.6%)	-
Difference of pain score compared with score prior to the first day[c] and after pain management, mean ±SD	- 1.2 ± 1.2	- 2.2 ± 0.8	0.0001
Range of difference of pain score	-2 to 0	-3.3 to -1	-

[a] For the first day, average of maximum pain score in every period from patients' self report. For the third day, average of maximum pain score in four periods on the third day of follow-up.

[b] Because patient's pain scores were not normal distributed.

[c] Average of maximum pain score 24 hours before pain management initiated on the first day, mean ±SD (Median ± IQR); 6.6 ± 2.3 (6.5 ± 5).

[d] Calculated from proportion of patients who received weak opioids and also received break-through analgesic for moderate pain.

[e] Calculated from proportion of patients who received strong opioids and also received break-through analgesic for severe pain.

[f] Wilcoxon Signed Ranks test p-value.

Table 4 Summary of maximum pain score differences prior to and after receiving pain management on the day of the follow-up in the naïve group.

Pain Scores Reduction	**The following group both days (Group I/I) n=52**	**The not following group both days (Group I/IV) n=64**
The first day difference of pain scores compared to prior to[a] and after[b] pain management, mean ±SD	- 2.6 ± 1.5	- 1.2 ± 1.2
The third day difference of pain scores compared to prior to[a] and after[c] Pain management, mean ±SD	- 3.9 ± 1.8	- 2.2 ± 0.8
p-value[d]	0.0001	0.0001

[a] Average of maximum pain score 24 hours before pain management initiated on the first day.

[b] Average of maximum pain score in every period after 2 hours of analgesics receiving from patients self assessment on the first day.

[c] Average of maximum pain score in four periods on the third day of follow-up.

[d] Sig (2-tailed) Mann-Whitney U-test p-value.

Comparison of pain management in the routine patients completely following WHO guideline and in the routine patients not following WHO guideline

Of the 102 patients in the routine group, 31.4% of patients (n=32) were classified as the routine patients following the WHO guideline on both days (Group II/I) and 35.3% of patients (n=36) were classified as the routine not following WHO both days (Group II/IV). In addition, 33.3% of patients (n=34) appeared to partially follow WHO including 5.9% of patients (n=6) following WHO only on day 1 (Group II/II) and 27.5% of patients (n=28) following WHO only on day 3 (Group II/III) as shown in Figure 2.

Among 32 patients in Group II/I, the maximum pain scores on average on the numerical rating scale (NRS) prior to and after first day of admission for pain management were 6.4 (SD±2.6) and 3.8 (SD±1.3), respectively. The mean difference of the pain score compared at time prior to and after first day of admission was decreased by 2.6 (SD±1.8). Most of the patients (53.1%, n=17) were in moderate pain and received pain management according to WHO. The majority of pain management assigned was in Step II (weak opioids) up to 59.4% (n=19) and all patients in this group received around-the-clock analgesics and strong opioids for break-through pain as shown in Table 5.

On the third day of admission, the maximum pain scores after receiving pain medication was 2.5 (SD±1.0). A mean difference of pain score compared at time prior to admission and after receiving pain management on the third day was reduced by 3.9 (SD±2.3). Almost all of the patients (81.3%, n=26) were in mild pain and 18.8%

of patients (n=6) were in moderate pain. The majority of pain management assigned was in Step II (weak opioids) up to 56.3% (n=18). All patients in this group also received around-the-clock analgesics and strong opioids for break-through pain regimen. There was a statistically significant difference in the decrease of pain score (-3.9, SD±2.3; p-value < 0.0001) on the third day of admission compared to the decrease of pain scores (-2.6, SD±1.8) on the first. These decreased pain scores might have been of clinical significance if they downstaged the pain severity scale based on WHO three step ladders.

Table 5 Summary of pain management in the routine group (Group II/I) who followed the WHO guideline on both days; n=32.

Variables	Day of follow-up		p-value[g]
	First Day	Third day	
Average of maximum pain after pain management initiated,[a] mean ±SD (Median ± IQR)[b]	3.8 ± 1.3 (4±1.7)	2.5 ± 1.0 (2.5±2)	0.0001
Type of pain severity			
Mild, n (%)	4 (12.5%)	26 (81.3%)	-
Moderate, n (%)	17 (53.1%)	6 (18.8%)	-
Severe, n (%)	11 (34.4%)	-	-
Type of pain management			
Step I (non-opioids)	1 (3.1%)	1 (3.1%)	-
Step II (weak opioids)	19 (59.4%)	18 (56.3%)	-
Step III (strong opioids)	12 (37.5%)	13 (40.6%)	-
Interval of pain management administration			
Around-the-clock	32 (100%)	32 (100%)	-
As-needed	-	-	-
Use of break-through pain analgesic for moderate pain	1 (5.2%)[d]	-	-
Use of break-through pain analgesic for severe pain	12 (100%)[e]	13 (100%)[e]	-
Difference of pain score compared with score prior to the first day[c] and after pain management, mean ±SD	- 2.6 ± 1.8	- 3.9 ± 2.3[f]	0.0001
Rang of difference of pain score	-4 to -1	-6.5 to -2.1	-

[a] For the first day, average of maximum pain score in every period from patients' self report. For the third day, average of maximum pain score in four periods on the third day of follow-up.

[b] Because patient's pain scores were not normal distributed.

[c] Average of maximum pain score 24 hours before pain management initiated on the first day, mean ±SD (Median ± IQR); 6.4 ± 2.6 (6 ± 5).

[d] Calculated from proportion of patients who received weak opioids and also received break-through analgesic for moderate pain.

[e] Calculated from proportion of patients who received strong opioids and also received break-through analgesic for severe pain.

[f] Clinical significance (> 3 points): Clinical significance is observed after pain score reduced greater than 3 points (Thienthong et al., 2006).

[g] Wilcoxon Signed Ranks test p-value.

Of the 36 patients in Group II/IV, the maximum pain scores prior to and after receiving medication for pain on the first day were 7.2 (SD±2.8) and 6.1 (SD±2.6), respectively. These appeared to be elevated than those reported in Group II/I. A mean difference of the pain scores compared at time prior to and after admission was decreased by 1.0 (SD±2.3). Most patients (66.6%, n=24) were in severe pain and majority of pain management assigned was in Step III (strong opioids) up to 58.3% (n=21). 83.3% of patients in this group also received around-the-clock analgesics and 9.5% of patients had received strong opioids for break-through pain as illustrated in Table 6.

On the third day of admission, the maximum pain score on average after receiving medication for pain was 4.0 (SD±2.5). A mean difference of the pain score compared at time prior to admission and after receiving pain management on the third day was reduced by 3.1 (SD±2.8) as compared to a pain score reduction of 3.9 (SD±2.3) reported in Group II/I. There were 47.2% of patients (n=17) in mild pain compared to 81.3% of those reported in Group II/I. The majority of pain management assigned was in Step III (strong opioids) up to 66.7% (n=24). 80.6% of patients in this group received around-the-clock analgesics regimen and only 4.1% of patients received strong opioids for break-through pain. There was a statistically significant difference in the decrease of pain score (-3.1, SD±2.8; p-value < 0.0001) on the third day of pain management when compared to pain scores (-1.0, SD±2.3) on the first day of pain management. These decreased pain scores were of clinical significance if they appeared to decrease pain intensity scale based on WHO to a lessen degree. The summary of pain management comparison in the routine patients completely following WHO guideline (Group II/I) and in the routine patients not following WHO guideline (Group II/IV) was illustrated in Table 7.

Table 6 Summary of pain management in the routine group (Group II/IV) who did not follow the WHO guideline on both days; n=36.

Variables	Day of follow-up		p-value[f]
	First Day	Third day	
Average of maximum pain after pain management initiated,[a] mean ±SD (Median ± IQR)[b]	6.1 ± 2.6 (6±3.3)	4.0 ± 2.5 (3.5±2.6)	0.0001
Type of pain severity			
Mild, n (%)	6 (16.7%)	17 (47.2%)	-
Moderate, n (%)	6 (16.7%)	12 (33.3%)	-
Severe, n (%)	24 (66.6%)	7 (19.4%)	-
Type of pain management			
Step I (non-opioids)	5 (13.9%)	5 (13.9%)	-
Step II (weak opioids)	10 (27.8%)	7 (19.4%)	-
Step III (strong opioids)	21 (58.3%)	24 (66.7%)	-
Interval of pain management administration			
Around-the-clock	30 (83.3%)	19 (80.6%)	-
As-needed	6 (16.7%)	7 (19.4%)	-
Use of break-through pain analgesic for moderate pain	-	-	-
Use of break-through pain analgesic for severe pain	2 (9.5%)[d]	1 (4.1%)[d]	-
Difference of pain score compared with score prior to the first day[c] and after pain management, mean ±SD	- 1.0 ± 2.3	- 3.1 ± 2.8[e]	0.0001
Rang of difference of pain score	-2.3 to 0	-5.3 to -1.5	-

[a] For the first day, average of maximum pain score in every period from patients' self report. For the third day, average of maximum pain score in four periods on the third day of follow-up.

[b] Because patient's pain scores were not normal distributed.

[c] Average of maximum pain score 24 hours before pain management initiated on the first day, mean ±SD (Median ± IQR); 7.2 ± 2.8 (8 ± 5).

[d] Calculated from proportion of patients who received strong opioids and also received break-through analgesic for severe pain.

[e] Clinical significance (> 3 points): Clinical significance is observed after pain score reduced greater than 3 points (Thienthong et al., 2006).

[f] Wilcoxon Signed Ranks test p-value.

Table 7 Summary of maximum pain score differences prior to and after receiving pain management on the day of the follow-up in the routine group.

Variables	The following group both days (Group II/I) n=32	The not following group both days (Group II/IV) n=36
The first day difference of pain score compared to prior to[a] and after[b] pain management, mean ±SD	- 2.6 ± 1.8	- 1.0 ± 2.3
The third day difference of pain score compared to prior to[a] and after[c] Pain management, mean ±SD	- 3.9 ± 2.3	- 3.1 ± 2.8
p-value[d]	0.0001	0.0001

[a] Average of maximum pain score 24 hours before pain management initiated on the first day.

[b] Average of maximum pain score in every period after 2 hours of analgesics receiving from patients self assessment on the first day.

[c] Average of maximum pain score in four periods on the third day of follow-up.

[d] Sig (2-tailed) Mann-Whitney U-test p-value.

Adverse Events

Of 183 patients who received opioids on the first day, 28.9% of patients (n=53) were prescribed medication for constipation prophylaxis while 71.1% of patients (n=130) did not receive any constipation prophylactic regimen. Of these 130 patients 37.2% (n=35) experienced constipation. However, constipation was resolved in 37.1% of patients reporting symptoms as they eventually received.

On the third day of admission, the incidence of constipation was reported in 77.8% of patients compared to 70.1% on day 1. However, more patients 35.4% (n=72) received constipation prophylaxis. For 64.6% (131) of patients who were not prescribed prophylaxis, 39.6% (n=20) of patients experienced constipation which was resolved in 38.8% (n=21) as they received laxative. The study results demonstrated that the most common adverse events from opiod analgesic treatments were constipation. The incidence of constipation had increased as a result of longer duration of treatment and perhaps from dose escalation as exhibited in Table 8.

Table 8 Incidence of constipation in 261 patients receiving pain management at Srinagarind Hospital.

Treatment	First day[a]	Third day [b]
	%	%
With opioids analgesic	70.1% (183/261)	77.8 (203/261)
With constipation prophylaxis	28.9% (53/183)	35.4% (72/203)
Despite constipation prophylaxis	-	2.6 (2/72)
Without constipation prophylaxis	37.2% (35/130)	39.9 (52/131)
Resolved with laxative	37.1% (13/35)	38.8% (21/54)

[a] Followed in 24 hours after staring analgesics on the first day of pain management in the hospital.

[b] Followed in 24 hours after starting analgesics on the third day of pain management in the hospital.

Discussion and conclusion

The World Health Organization (WHO) has recommended guidelines for cancer pain by utilizing pain intensity as the primary resource for specifying treatment. Principal analgesic drugs were modified from the group of non-opioids analgesic drugs for patients with mild to moderate pain to weak opioid for patients with moderate pain and to more potent or strong opioids for patients with severe pain. The use of analgesic drugs is the mainstay of cancer pain management. This cross sectional study aimed to explore the result of cancer pain management at Srinagarind Hospital after the establishment of WHO pain guideline.

Our results (Table 1) showed that at one week prior to admission most patients had an average pain score of 6.0 (SD±2.6) which could be defined as moderate pain according to WHO. As for the level of pain intensity within 24 hours prior to admission, our results found that 47.9% of patients (n=125), 40.6% of patients (n=106) and 11.5% of patients (n=30) were in severe, moderate and mild pain, respectively. Most common type of pain experienced by our studied patients was somatic, neuropathic and visceral pain. In addition, these patients taken some type of pain medications described as NSAIDs (27.6%, n=72), weak opioids (36.0%, n=94) and strong opioids (13.4%, n=35), respectively. Considering the high proportion of patients experiencing a severe pain and low proportion of strong opioids usage, this conferred an inappropriate pain management prior to admission.

Upon admission, the difference of pain score prior to and after receiving pain management between the first day and the third day of follow-up within same patient's group were found to decrease significantly from baseline in all groups of patients (p-values < 0.0001). Our study results demonstrated that cancer patients in the naïve group who received analgesics following the WHO guideline on both days (Group I/I) had better decreased pain scores (2.6±1.5) compared to a minimal decreased pain scores (1.2±1.2) in the group not following the WHO guideline on both days (Group I/IV) on the first day with the similar result on third day. Furthermore, the comparable results were also seen in the routine group (Group II/I, II/IV). Nonetheless, those patients

not following WHO (Group I/IV, II/IV) appeared to received sup-optimal pain management as they were less likely to receive around-the-clock and medication for breakthrough pain.

In conclusion, the results also illustrated that the pain intensity was significantly decreased within the first three days after pain management was initiated. The differences decreased pain scores on the third day of most groups of patients appeared to be of clinical significance. In addition, the study results show that the pain scores of cancer patients who received analgesics following the WHO guideline were decreased more than those who did not receive analgesics following the WHO guideline. The findings from this present study will provide overview information about current practical treatment of cancer pain and address the importance of implementing the WHO pain management guidelines into daily practice. Oncology pharmacists should pay more attention on supportive pain issues and encourage health care providers to deliver adequate pain control through effective pharmaceutical care strategy.

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