한국임상약학회지 제33권 제1호
Korean J Clin Pharm, Vol. 33, No. 1, pp. 43–50, 2023

Original Article

Korean Journal of Clinical Pharmacy
Official Journal of
Korean College of Clinical Pharmacy
pISSN 1226-6051 eISSN 2508-786X
https://doi.org/10.24304/kjcp.2023.33.1.43

Comparison of Fentanyl-Based Rapid Onset Opioids for the Relief of Breakthrough Cancer Pain: Drug Price Based on Effect Size

Seongchul Kim[1†], Hayoun Jung[1†], Jina Park[1], Jinsol Baek[1], Yeojin Yun[1], Junghwa Hong[1], and Eunyoung Kim[1,2*]

[1]Department of Pharmaceutical Industry, Chung-Ang University, Seoul 06974, Republic of Korea
[2]Clinical Data Analysis, Evidence-Based Clinical Research Laboratory, Departments of Health Science & Clinical Pharmacy, College of Pharmacy, Chung-Ang University, Seoul 06974, Republic of Korea

ABSTRACT

Background and Objective: With the advancement of cancer treatments and increased life expectancy, managing breakthrough cancer pain (BTcP) is essential to improve the quality of life for cancer patients. This study aimed to compare the major rapid onset opioids in Korea based on their characteristics and costs to determine the best option for each patient. **Methods:** Based on sales information from IQVIA-MIDAS, sublingual fentanyl tablet (SLF), fentanyl buccal tablet (FBT), and oral transmucosal fentanyl citrate (OTFC) were selected as the top three drugs for the treatment of BTcP in Korea, considering them the most comparable drugs. The cost and cost-pain relief ratio of the drugs for short-term (1 month) and long-term (1 year) treatment were compared and the ease of administration based on various factors, including pharmacokinetics, onset of action, and administration procedures were evaluated. **Results:** SLF was evaluated as the best overall in terms of rapid onset of action, ease of administration, and drug cost and also had the highest market share. SLF had the lowest cost pain relief ratio for both the initial and supplemental treatment for the 1-month pain intensity difference 15 (PID15) ratio. However, for the 1-month PID30 ratio, SLF was not superior to OTFC or FBT. The longer the breakthrough cancer pain duration, the more cost-effective the other rapid onset opioids. **Conclusion:** The rapid onset opioids that fit the patient's breakthrough cancer pain pattern have the best cost-effectiveness.

KEYWORDS: Breakthrough cancer pain, rapid onset opioids

Although the survival rate of cancer patients continues to rise due to early diagnosis and the new treatments, cancer patients still experience mental and physical challenges and cancer pain is one of their common difficulties.[1)] Breakthrough cancer pain (BTcP) is defined as a transient exacerbation of pain that occurs spontaneously, or in connection with a certain trigger predictable or unpredictable, despite stable and well controlled background pain.[2)] The recent study with 956 cancer patients in 33 hospitals in Korea reported that 73% of patients experienced BTcP and in another study for 1,000 cancer patients, about 90% experienced BTcP, which interfered with their daily activities.[3,4)]

Recent medical guidelines recommend the active use of narcotic analgesics at all stages of pain.[5)] As BTcP is characterized by rapid deterioration within 5-10 minutes and a short duration within 30-60 minutes, it is necessary to choose a drug that shows the best efficacy and fewer adverse reactions, taking into account the time to reach the maximum

†The first two authors contributed equally to this work.

*Correspondence to: Eunyoung Kim, Department of Pharmaceutical Industry, Chung-Ang University, Seoul 06974, Republic of Korea
Clinical Data Analysis, Evidence-Based Clinical Research Lab., Departments of Health Science & Clinical Pharmacy, College of Pharmacy, Chung-Ang University, Seoul 06974, Republic of Korea
Tel: +82-2-820-5791, Fax: +82-2-816-7339, E-mail: eykimjcb777@cau.ac.kr

Received 7 December, 2022; Revised 13 February, 2023; Accepted 13 February, 2023

Table 1. Search key term

Title	Term
Efficacy	breakthrough cancer pain, breakthrough pain, fentanyl, transmucosal fentanyl, rapid onset opioid, cost, 돌발성 암성 통증, 돌발성 통증(only for Korean study)
BTcP characteristics of Korean patients	breakthrough cancer pain, breakthrough pain, transmucosal fentanyl, rapid onset opioid, korea, 돌발성 암성 통증, 돌발성 통증(only for Korean study)
Ease of administration	breakthrough cancer pain, breakthrough pain, fentanyl, preference, selection, administration, ease, 돌발성 암성 통증, 돌발성 통증(only for Korean study)

BTcP, breakthrough cancer pain

intensity and the duration of the pain.[6] Rapid onset opioids (ROO) are indicated for breakthrough pain management in cancer patients who are already receiving and tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. A total of 7 ROOs have been launched in Korea (Jan 2021), and 5 of which are orally administered drugs. (Supplementary Table 1)

A study analyzing the patient sample data of the National Health Insurance Service from 2010 to 2013 found that the opioid use per cancer patient increased dramatically at an average annual rate of 54%.[7] ROO usage also increased by about 7% in 2011 compared to 2008. According to Integrated Quality Insights and Analytics (IQIVIA) ROO market data (Q3 2020), the market in 2020 showed a growth rate of 35% compared with 2016.[8,9]

Although interest in BTcP and the use of ROO have been increasing, there are no comparative data on drugs reflecting the Korean situation. This study aims to provide an objective index for selecting optimal ROOs for an individual by reflecting the BTcP patterns and economic circumstances of Korean patients.

Materials and Methods

Selection of drugs for research

Domestic ROO sales data up to September 30, 2020 was obtained from the IQVIA Multinational Integrated Data Analysis System (IQVIA-MIDAS) database (N02A Non-narcotic analgesics). IQVIA-MIDAS dataset is based on sales data from manufacturers (direct sales) and wholesalers, or sales data obtained from hospitals and retail pharmacies and IQVIA-MIDAS database for Korea has 100% market coverage. IQVIA-MIDAS data has been validated from alternative sales data sources and used to assess global pharmaceutical consumption patterns.[10]

According to IQIVIA ROO market data, there were five comparable drugs (market share %): sublingual fentanyl tablet (57%), fentanyl buccal citrate (29%), oral transmucosal fentanyl citrate (8%), intranasal fentanyl spray (6%), and sublingual fentanyl tablet generic (1%). ROOs with less than 5% of market share and parenterally administrated drugs were excluded following the Korean guidelines recommending oral administration first.[9,11] The following three drugs were finally selected for comparison: sublingual fentanyl tablet (SLF), fentanyl buccal tablet (FBT), and oral transmucosal fentanyl citrate (OTFC).

Literature search

The characteristics and drug prices of selected drugs were collected from the Integrated Drug Information System of the Ministry of Food and Drug Safety by searching the brand name (OTFC: Actiq®, FBT: Fentora®, SLF: Abstral®).

PubMed and ScienceOn were used to search overseas and Korean research, respectively, and the search terms are shown in (Table 1). Topics of literature search were selected as the effect of the drugs, the characteristics of BTcP in Korean patients, and the ease of administration. The literature adopted as an effective value of the study on the cost-effectiveness ratio of ROO drugs was applied to this study, the cost of pain relief ratio was calculated by reflecting the BTcP characteristics of Korean patients, and convenience of administration was further considered based on a survey of Korean medical staff.[12] Studies on the characteristics of BTcP in Korean patients before 2017 were excluded as there was little interest in and use of ROOs for BTcP management.

Comparison

Cost

- Since BTcP is treated simultaneously with cancer and

background pain, this study assumes that there is no additional cost for BTcP treatment.
- The treatment cost for the short-term (1 month) and the long-term (1 year) treatment was compared.

Cost pain relief ratio[13,14)]

- The initial ratio was defined as the drug cost per person required when 100% of patients have pain controlled.
- Supplemental ratio was defined as average drug cost per person, reflecting some patients who obtained adequate analgesia with the first dose and other patients who continued to treat with the second dose from the second episodes due to lack of efficacy of the first dose.
- Cost pain relief ratio was compared based on the pre-defined formula

$$\frac{\text{Superior cost} - \text{other drugs cost}}{\text{Superior PID (Pain intensify difference)} - \text{other drugs PID}}$$

Ease of administration

Pharmacokinetic profile, onset of action, transmucosal absorption rate, administration procedure, treatment interval, dose, appearance, size, packaging unit, use by date, manufacturing country, storage condition, and disposal method were compared.

Results

Comparison of characteristics and drug cost

The three ROO drugs for breakthrough cancer pain differ in terms of administration procedure, application site, and interval between doses. OTFC, FBT, and SLF all have four or more dose strengths, but differ in their shape, size, and method of administration. OTFC is a solid drug matrix on a handle and should be consumed over 15 minutes by moving the matrix from one side of the cheek to the other using a handle and sucking, not chewing. FBT is round tablets and should be placed above the most posterior molars and not chewed, sucked, or swallowed. Sublingual administration is possible as an alternative route and the recommended administration time is 14-25 minutes. SLF is different in shape for each strength and should be completely dissolved under the tongue without chewing, sucking, or swallowing. The interval between administrations is 4 hours for OTFC and FBT and 2 hours for SLF.

OTFC has a long axis of 95 mm, short axis of 10 mm, and thickness of 18 mm, while FBT measures 6 mm×6 mm×1.7 mm and SLF measures 6 mm×6 mm×2 mm. OTFC and FBT are manufactured in the United States and have a shelf life of months from the manufacturing date, while SLF is manufactured in the UK and should be stored below 25°C with a shelf life of 24 months. The packaging unit is 30 tablets for OTFC and SLF and 28 tablets for FBT.

Table 2. Comparison of drug cost

	OTFC	FBT	SLF
100 mcg		KRW 4,911	KRW 3,781
200 mcg	KRW 7,367	KRW 7,367	KRW 5,673
300 mcg			KRW 6,062
400 mcg	KRW 7,873	KRW 7,873	KRW 6,062
600 mcg	KRW 7,934	KRW 7,934	
800 mcg	KRW 9,125	KRW 9,125	

OTFC: Oral transmucosal fentanyl citrate, SLF: Sublingual Fentanyl tablet, FBT: Fentanyl buccal tablet (MFDS, 2021.01)

The pharmacokinetic profiles of these ROO drugs also vary. The median Tmax of the initial dose is 40 minutes for OTFC, 45 minutes for FBT, and 30 minutes for SLF. The median Tmax of the second dose is 25 minutes for OTFC, 40 minutes for FBT, and 52 minutes for SLF. The transmucosal absorption rate is 25% for OTFC, 48% for FBT, and 54% for SLF[15)], and the onset time is 15-30 minutes for OTFC, 15 minutes for FBT, and 10 minutes for SLF.[16)]

In terms of drug cost, SLF had the lowest cost followed by FBT and OTFC. At the initial dose, FBT and SLF had 67% and 51% cost comparison with OTFC, respectively (Table 2).

The 1-month cost for initial doses of OTFC, FBT, and SLF was around KRW 660,000, KRW 440,000, and KRW 340,000, respectively. FBT was approximately KRW 220,000 less expensive than OTFC and SLF was KRW 320,000 less expensive. The 1-month cost for second doses of OTFC, FBT, and SLF was approximately KRW 700,000, KRW 660,000, and KRW 510,000, respectively. FBT was around KRW 40,000 less expensive than OTFC and SLF was approximately KRW 190,000 less expensive.

The 1-year cost for initial doses of OTFC, FBT, and SLF was approximately KRW 8,000,000, KRW 5,300,000, and KRW 4,100,000, respectively. FBT was around KRW 2,700,000 less expensive than OTFC and SLF was approximately KRW 3,900,000 less expensive. The 1-year cost for second doses of OTFC, FBT, and SLF were around KRW 8,600,000, KRW 8,000,000, and KRW 6,200,000, respectively. FBT was

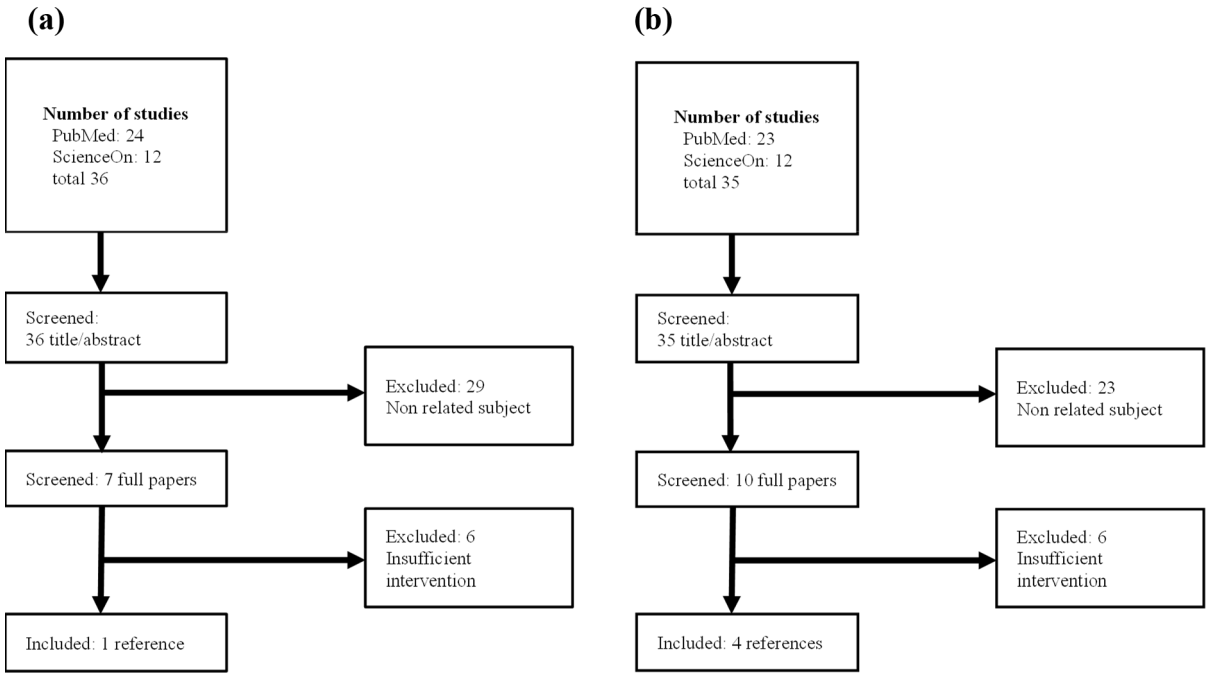


Fig. 1. Flow chart of study selection for efficacy and BTcP characteristics of Korean patients. BTcP, breakthrough cancer pain

approximately KRW 600,000 less expensive than OTFC and SLF was around KRW 2,400,000 less expensive.

Comparison of cost pain relief ratio

The effect value was benchmarked from one meta-analysis that indirectly compared Randomized clinical trials of each drug available to date[17,18] (Fig. 1a).

Four studies were finally selected for the patterns of BTcP in Korean patients, the time horizon and number of times that were the most frequent were selected because the reference point was different for each study (Fig. 1b). It was assumed that the BTcP of Korean patients lasted for 30 minutes and occurred three times a day. For PID15, which is pain intensity difference (PID) relative to placebo at 15 minutes after administration of each drug, OTFC was 0.46, FBT was 0.51, and SLF was 0.53. For PID30, which was PID relative to placebo at 30 minutes after administration, OTFC was 1.01, FBT was 0.96, and SLF was 0.83.

For the Initial ratio of 1-month PID15, the OTFC is KRW 1,441,370, FBT is KRW 866,647 and SLF is KRW 642,057. Initial ratio of 1-year PID15 is KRW 17,536,663 for OTFC, KRW 10,544,206 for FBT, and KRW 7,811,689 for SLF. For 1-month PID30, OTFC is KRW 656,465, FBT is KRW 460,406 and SLF is KRW 409,988. Initial ratio of 1-year PID30 is KRW 7,986,995 for OTFC, KRW 5,601,609 for FBT and KRW 4,988,187 for SLF (Fig. 2a).

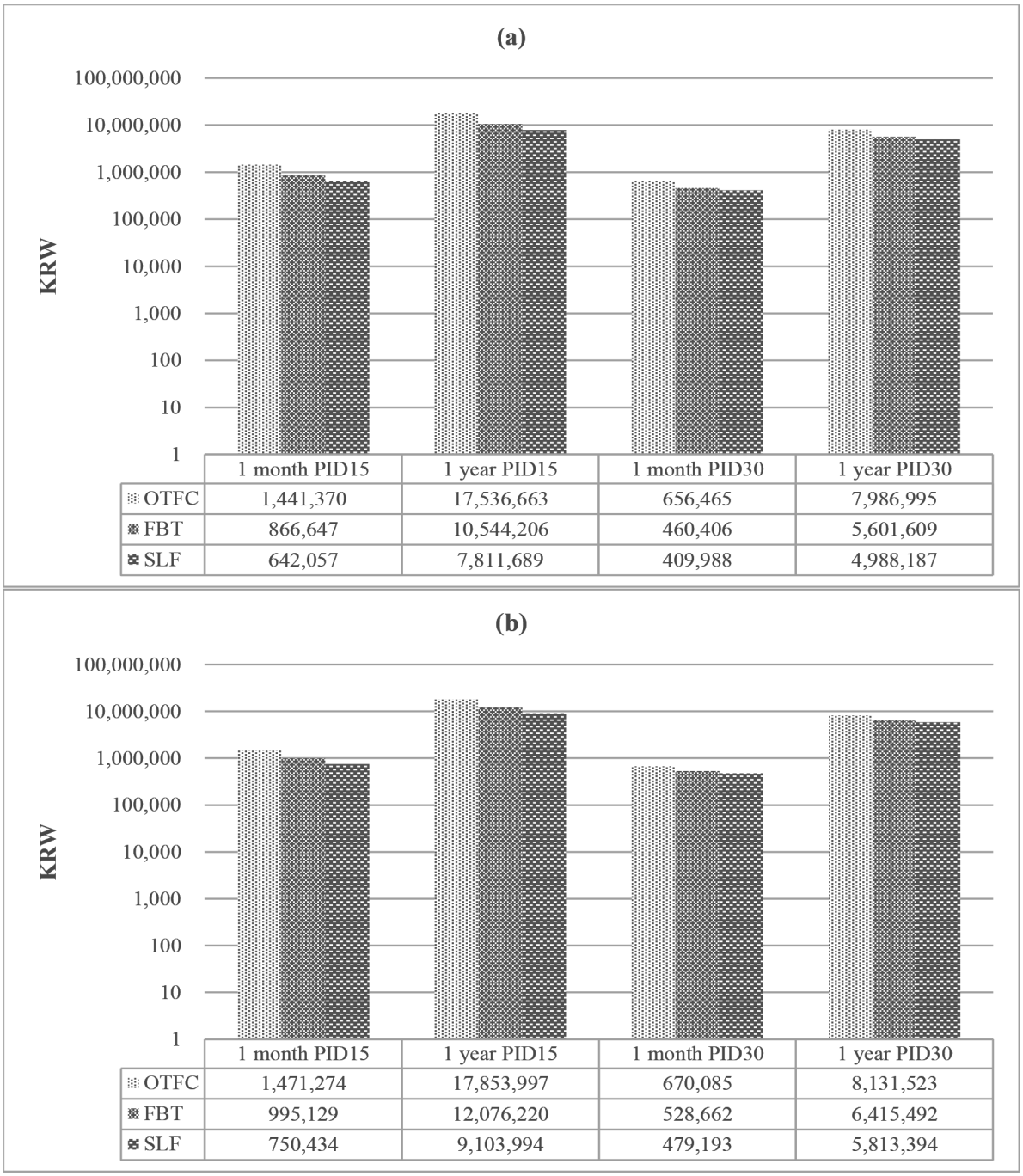
The difference of the Initial ratio of 1-month PID15 between OTFC, the most expensive drug, and SLF, the cheapest drug, is about KRW 800,000, and the difference for 1 year is about KRW 9,700,000. The maximum difference of 1-month PID30 is about KRW 250,000, and 1-year PID30 is about KRW 3,000,000.

The rescue medication usage ratios relative to placebo required for supplemental ratio comparison were 0.26, 0.29, and 0.33 in the order of OTFC, FBT, and SLF, respectively.

The Supplemental ratio of 1-month PID15 was KRW 1,471,274 for OTFC, KRW 995,129 for FBT and KRW 750,434 for SLF. The supplemental ratio for 1-year PID15 is KRW 17,853,997 for OTFC, KRW 12,076,220 for FBT and KRW 9,103,994 for FBT. The Supplemental ratio of 1-month PID30 is KRW 670,085 for OTFC, KRW 528,662 for FBT and KRW 479,193 for SLF. The Supplemental ratio of 1-year PID30 is KRW 8,131, 523 for OTFC, KRW 6,415,492 for FBT and KRW 5,813,394 for SLF (Fig. 2b).

The difference of the supplemental ratio of 1-month PID15 between OTFC and SLF is about KRW 720,000, and the difference for 1 year is about KRW 8,700,000. The maximum difference of 1-month PID30 is about 190,000 won, and 1-year PID30 about KRW 2,300,000.

For both the initial and supplemental ratio of PID15, SLF



	1 month PID15	1 year PID15	1 month PID30	1 year PID30
OTFC	1,441,370	17,536,663	656,465	7,986,995
FBT	866,647	10,544,206	460,406	5,601,609
SLF	642,057	7,811,689	409,988	4,988,187

	1 month PID15	1 year PID15	1 month PID30	1 year PID30
OTFC	1,471,274	17,853,997	670,085	8,131,523
FBT	995,129	12,076,220	528,662	6,415,492
SLF	750,434	9,103,994	479,193	5,813,394

Fig. 2. Comparison of Initial ratio and Supplemental ratio. OTFC: Oral transmucosal fentanyl citrate, SLF: Sublingual Fentanyl tablet, FBT: Fentanyl buccal tablet, PID, pain intensity difference

showed superiority to OTFC or FBT. However, for PID30 SLF did superiority over OTFC or FBT (Table 3).

Ease of administration

There were two overseas studies (Supplementary Fig. 1). The first study assessed ease of access and administration, palatability and overall impression after 30 cancer patients took a placebo of FBT, SLF, and Intranasal fentanyl spray (INFS).[18] The dissolution time was 57 seconds for SLF (median, 37-72) and 323 seconds for FBT (median, 186-443). SLF had 20 positive feedbacks relating to the convenience, and FBT had 18 negative feedbacks. The most preferred drugs

Table 3. Comparison of the best drug and the rest

initial ratio		SLF	supplemental ratio	
Month	Year	Vs OTFC	Month	Year
-4,610,571	-56,095,286	PID_{15}	-3,986,510	-48,396,024
1,793,000	21,814,833	PID_{30}	1,550,309	18,820,676
		Vs FBT		
-5,085,000	-61,867,500	PID_{15}	-5,489,283	-66,687,753
782,308	9,518,077	PID_{30}	844,505	10,259,654

OTFC: Oral transmucosal fentanyl citrate, SLF: Sublingual Fentanyl tablet, FBT: Fentanyl buccal tablet, PID, pain intensity difference

were SLF, INFS, and FBT.

The second study compared seven ROOs using the system of objectified judgment analysis (SOJA), an objective evaluation and analysis system for rational drug selection.[19] Among the 7 assessment items, for ease of use, the highest scores were in the order of SLF, FBT, and OTFC.

As a result of analyzing the two selected studies, SLF was the most convenient, followed by FBT and OTFC.

Discussion

In this study, the pain relief rate was calculated and compared by reflecting the characteristics of three oral ROO drugs with a high proportion of domestic sales, the drug cost according to the duration of administration, and the BTcP pattern of domestic patients. In the selection of ROO drugs, important factors such as drug efficacy, drug price, and ease of administration seem to be reflected in the actual market. At PID15, SLF has a shorter onset time, faster Tmax and higher transmucosal absorption than the other two drugs, making it suitable for BTcP with rapid onset and short duration. However, at PID30, other drugs are more cost-effective than SLF. When selecting ROO drugs in BTcP patients, it is necessary to use drugs that fit the patient's BTcP pattern.

In a previous study conducted in South Korea, it was found that intranasal fentanyl spray was more cost-effective compared to oral transmucosal fentanyl citrate (OTFC)[20] However, this current study showed that sublingual tablets, which were approved after the previous study, were more cost-effective compared to the other two drugs. In a separate cost-effectiveness study conducted in Italy, intranasal fentanyl spray was found to be more cost-effective than oral transmucosal fentanyl citrate and buccal fentanyl tablets.[21] However, a direct comparison is challenging as the study did not include sublingual fentanyl (SLF), which has the largest market share in South Korea.

Through this process, it was intended to be an objective reference data for ROO selection in Korea. This study is significant in that it reflects drugs launched in Korea and applies the BTcP pattern of domestic patients based on recent domestic studies, unlike previous studies in Korea. Nevertheless, we would like to describe the limitations found in the progress of this study.

First, this study relied on only one indirect comparative study for the effective value of each drug as there were limited number of studies on BTcP in Korean patients and studies comparing several drugs. The selected study as a reference of effect value in this study was meta-analysis that indirectly compared Randomized Controlled Trial (RCT) studies of each drug available to date, however, the number of studies included for each drug was at most 3.[19]

Second, there was a limitation on the actual number of doses. This study aimed to reflect the BTcP characteristics of Korean patients to the drug cost. In overseas studies, BTcP reached peak pain within 5 to 10 minutes, lasted about 30 to 60 minutes, and occurred 3 to 4 times a day. There was no significant difference in Korean patients.[8] Based on Korean studies, this study assumed that cancer patients take ROO drugs three times a day, and cost pain relief ratio was compared for 1 month and 1-year periods.[22-25] Patients who take ROO for the first time should have the titration period but it was applied to the first episode only.

Third, since there become many options for BTcP treatment, not only the effects of drugs but also the economic aspects are important for selecting ROO drugs. The previous study reported that both the medical staff and patients wanted to discuss the treatment cost, and 68% of patients answered that they would like to discuss the medical cost first before choosing a treatment.[14] The direct and indirect costs for the

overall treatment of cancer patients were not included because the BTcP is treated simultaneously with the treatment of cancer and background pain, but additional medical costs due to severe BTcP should be considered.

Korean studies on the use of opioids are steadily increasing due to widespread awareness of the importance of pain management, however, the research subjects on BTcP are limited. A future study that reflects the limitations of this study will provide the more concrete rationale for ROO drug selection.

Conclusion

In this study, cost pain relief ratio was calculated and compared according to the characteristics of the following ROO drugs: oral transmucosal fentanyl citrate, fentanyl buccal tablet, and sublingual fentanyl tablet. Cost pain relief ratio at 15- and 30-minute post dose reflecting the real-world situation, showed the lowest drug cost for SLF in both initial and supplementary ratio, while SLF was evaluated as being the best in ease of administration. The ROO that occupies the highest market share is SLF, which is consistent with the results of this study. To help the treatment of BTcP in cancer patients in the future, more detailed studies reflecting direct and indirect costs should be conducted to provide additional information on the most cost-effective drugs.

Conflicts of Interest

The authors have no conflicts of interest to declare with regards to the contents of this study.

References

1. National cancer center, cancer trend report 2021. Available from https://cancer.go.kr/download.do?uuid=71610cce-c1a7-457d-8ee6-09c93aacb330.pdf. Accessed February 25, 2023.
2. Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. Eur J Pain 2009; 13(4):331-8.
3. Koh S, Lee K, Oh S, Kang J, *et al*. Assessment, management, and barriers of breakthrough cancer pain: a nationwide study in Korea. Support Care Cancer 2019;27:eP064.
4. Davies A, Buchanan A, Zeppetella G, *et al.* Breakthrough Cancer Pain: An Observational Study of 1000 European Oncology Patients. J Pain Symptom Manage. 2013;46(5):619-28.
5. Bae SB, Lee SC. Medical Treatment of Cancer Pain: Drug Therapy according to Guidelines Will Improve the Quality of Life of Cancer Patients. Korean J Med 2018;93(3):260-5.
6. Bennett D, Burton AW, Fishman S, Fortner B, *et al*. Consensus panel recommendations for the assessment and management of breakthrough pain: Part 2 Management. P and T. 2005;30(6):354-61.
7. HiNeca [Vol.65] Abuse of opioid, are we safe? Available from https://hineca.kr/1976 Accessed November 05 2022.
8. Min Seok Seo, Jae Yong Shim Breakthrough Cancer Pain. Korean J Hosp Palliat Care 2015;18(1):1-8.
9. IQVIA. Quintiles and IMS Health. Available from https://www.iqvia.com/locations/korea. Accessed February 25, 2023.
10. Ju, C., Wei, L., Man, *et al*. Global, regional, and national trends in opioid analgesic consumption from 2015 to 2019: a longitudinal study. Lancet Public Health 2022;7(4):e335-46.
11. European Society for Medical Oncology. Cancer Pain Management Clinical Practice Guidelines 2018. Available from https://reference.medscape.com/viewarticle/902352. Accessed February 25, 2023.
12. Shin J, Shim JY, Seo MS, *et al.* Factors Influencing Pain Medication Preference for Breakthrough Cancer Patients and Their Application to Treatments: Survey on Physicians. Korean J Hosp Palliat Care 2018;21(1):9-13.
13. Mercadante S, Marchetti P, Cuomo A, Mammucari M, Caraceni A; IOPS MS study Group. Breakthrough pain and its treatment: critical review and recommendations of IOPS (Italian Oncologic Pain Survey) expert group. Support Care Cancer. 2016;24(2):961-8.
14. YS Rhee, SY Kim., JH Park. Financial Hardship Factors affecting the Cancer Patient's Quality of Life. Journal of the Korea Academia-Industrial cooperation Society. 2020;21(10):299-307.
15. Simon SM, Schwartzberg LS. A review of rapid-onset opioids for breakthrough pain in patients with cancer. J Opioid Manag. 2014; 10(3):207-15.
16. Cortesi PA, D'Angiolella LS, Vellucci R, *et al*. Cost-effectiveness analysis of oral fentanyl formulations for breakthrough cancer pain treatment. PLoS One. 2017;12(6):e0179523.
17. England R, Maddocks M, Manderson C, Zadora-Chrzastowska S, Wilcock A. How practical are transmucosal fentanyl products for breakthrough cancer pain? Novel use of placebo formulations to survey user opinion. BMJ Support Palliat Care. 2011;1(3):349-51.
18. Janknegt R, van den Beuken M, Schiere S, *et al*. Rapid acting fentanyl formulations in breakthrough pain in cancer. Drug selection by means of the System of Objectified Judgement Analysis. Eur J Hosp Pharm. 2018;25(3):e2.
19. Zeppetella G, Davies A, Eijgelshoven I, Jansen JP. A network meta-analysis of the efficacy of opioid analgesics for the management of breakthrough cancer pain episodes. J Pain Symptom Manage. 2014; 47(4):772-85.
20. Hayan Kwon. Cost-effectiveness analysis of opioid analgesics for treatment of breakthrough pain in cancer patients. M.S Thesis for Seoul National University Graduate School. 2012.
21. Giuliani J, Fiorica F, Sacchetto A, Franceschini G, Vaccari F, Bonetti A. The role of fentanyl in the treatment of breakthrough cancer pain: Different biotechnologies, different results and different drug costs. J Oncol Pharm Pract. 2021;27(2):445-7.
22. Shin J, Cho SJ, Lee J, Choi YS. Validation of the Korean Version of the Breakthrough Pain Assessment Tool in Cancer Patients. J Pain Symptom Manage. 2017;54(3):361-7.
23. Kwon MY, Cho HN, Koo DH, Lee YG, Oh S, Lee SS. Initial titration with 200 μg fentanyl buccal tablets: a retrospective safety

analysis in Korean cancer patients. Korean J Intern Med. 2018; 33(3):577-84.
24. Choi YJ Factors associated with Breakthrough Pain in Cancer Patients, M.S Thesis for Kyung Hee University Graduate School. 2019.
25. Kang JH, Koh SJ, Oh SY, *et al*. Interference with daily functioning by breakthrough pain in patients with cancer. Support Care Cancer. 2020;28(11):5177-83.