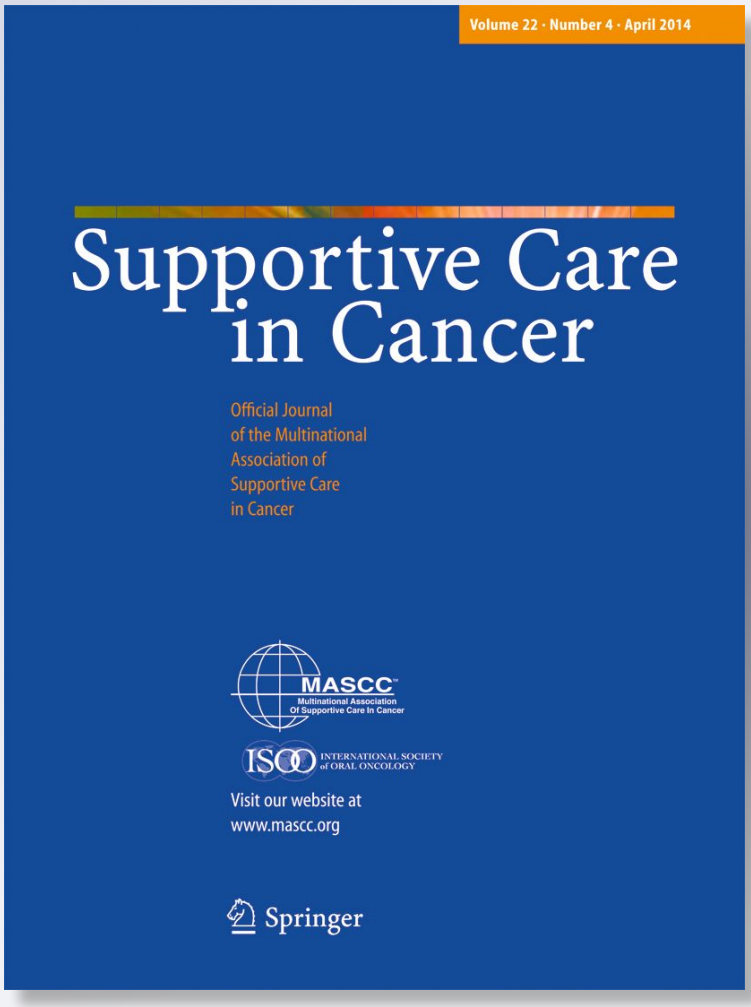
Comparison of efficacy of meperidine and fentanyl in terms of pain management and quality of life in patients with cervical cancer receiving intracavitary brachytherapy: a double-blind, randomized controlled trial

Saengrawee Thanthong, Sirikorn Rojthamarat, Wipra Worasawate, Phongthara Vichitvejpaisal, et al.

Supportive Care in Cancer

ISSN 0941-4355
Volume 25
Number 8

Support Care Cancer (2017)
25:2531-2537
DOI 10.1007/s00520-017-3662-3



Springer

Support Care Cancer (2017) 25:2531–2537
DOI 10.1007/s00520-017-3662-3

ORIGINAL ARTICLE

Comparison of efficacy of meperidine and fentanyl in terms of pain management and quality of life in patients with cervical cancer receiving intracavitary brachytherapy: a double-blind, randomized controlled trial

Saengrawee Thanthong[1] · Sirikorn Rojthamarat[1] · Wipra Worasawate[2] · Phongthara Vichitvejpaisal[3] · Danupon Nantajit[1] · Nantakarn Ieumwananontachai[1,4]

Received: 29 September 2016 / Accepted: 6 March 2017 / Published online: 18 March 2017

Abstract
Objective The aim of this study was to compare the effectiveness of two sedative regimens, a benzodiazepine with either meperidine or fentanyl, in relieving pain in patients with cervical cancer undergoing intracavitary brachytherapy in terms of pain score and quality of life.
Methods Forty unselected outpatients undergoing brachytherapy (160 fractions) were enrolled with informed consent and randomized to receive a benzodiazepine with either meperidine or fentanyl. The perceived pain score according to a standard 10-item numeric rating scale was collected every 15 min during the procedure, and the perceived quality of life was determined at the end of each procedure using the EuroQol five-dimension questionnaire. The patients and medical staff members directly involved with the procedure were blinded to the medication used.
Results The patients' pain levels were mild in both analgesic groups. Meperidine appeared to be slightly more effective than fentanyl, although the differences in the average pain score and quality of life were not statistically significant.
Conclusion Both meperidine and fentanyl in combination with benzodiazepine were effective in relieving pain and discomfort in patients undergoing brachytherapy.
Trial Registration NCT02684942, ClinicalTrials.gov

Keywords Brachytherapy · Meperidine · Fentanyl · Pain management · Quality of life

✉ Saengrawee Thanthong
saengrawee81@gmail.com

[1] Department of Radiation Oncology, Chulabhorn Hospital, Chulabhorn Royal Academy, 54 Kamphang Phet 6 Rd, Lak Si, Bangkok 10210, Thailand

[2] Department of Anesthesiology, Chulabhorn Hospital, Chulabhorn Royal Academy, Bangkok, Thailand

[3] Department of Anesthesiology, Siriraj Hospital, Mahidol University, Bangkok, Thailand

[4] Department of Radiology, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Introduction

Cervical cancer is a major health threat in developing countries and one of the most prevalent cancer types worldwide. Global cancer statistics estimated cervical cancer to be the fourth leading type of female cancer accounting for 527,600 new cases and 265,700 deaths in 2012, and 485,000 new cases and 236,000 deaths in 2013 [1, 2]. In 2016, in the USA, there were nearly 13,000 new cases and 4120 deaths from the disease [3]. Cervical cancer is also more pronounced in developing countries, where human papilloma virus screenings could prove to be particularly useful in reducing the number of deaths [4].

Cervical cancer, similar to other non-communicable diseases, has substantial socioeconomic impacts and adversely affects patients' quality of life (QoL). Presently, the major treatment modality for stage 0 to IA cervical cancer is surgery. Concurrent chemoradiation is the standard practice for the other stages (IB to IVA) [5, 6]. Chemotherapy and radiotherapy also play a large role as palliative treatments in the management of advanced-stage cervical cancer [7, 8].

Radiation therapy for cervical cancer involves external beam radiotherapy and intracavitary brachytherapy. Brachytherapy is crucial in the treatment of cervical cancer and significantly improves patient survival [9, 10]. However,

this procedure can be extremely painful and laborious because the physician places the patient in the lithotomy position and inserts applicators through her cervix during a 15 to 30 min brachytherapy session. The whole process takes up to approximately 2 to 3 h, usually causing the patient distress. Pain is considered a major stress factor which causes posttraumatic stress disorder in patients undergoing brachytherapy [11]. As a result, the American Brachytherapy Society recommends that the procedure is performed under conscious sedation (intravenous analgesia), sedation (total intravenous anesthesia), regional analgesia (paracervical blockade or spinal analgesia), or general anesthesia [12]. However, there is no consensus regarding a standard sedation protocol for brachytherapy or which sedative medication is best suited for the procedure. Nearly 35% of brachytherapy procedures are currently performed under conscious sedation using regional anesthesia [13]. The benzodiazepines, a class of psychoactive drugs used to treat anxiety, insomnia, and a range of other conditions by enhancing the effects of neurotransmitters, are often used to alleviate stress and promote sleep in patients undergoing brachytherapy [14]. Meperidine is an opioid analgesic with pain-relieving properties. This drug is used to relieve moderate to severe pain, including pain during labor and pain before and during operations. However, intramuscular injection of meperidine appears to be ineffective for relieving pain during the brachytherapy procedure [15]. In contrast, fentanyl is often used in high-dose-rate brachytherapy for cervical cancer, especially in combination with midazolam [16, 17]. Either analgesic has been utilized with benzodiazepine, yet the properties and pharmacokinetics of these two analgesics are dissimilar. Both anesthetics have a clearance time of 3 to 8 h. Meperidine has an onset time of 10 to 15 min and a duration of action of 120 to 240 min. Fentanyl has a shorter onset time of 7 to 8 min and a duration of action of 30 to 60 min, which is shorter than the required duration for brachytherapy. Thus, the patient could experience pain after its action has ceased. In the present study, we compared the efficacy of meperidine and fentanyl in terms of pain relief and QoL in patients with cervical cancer receiving brachytherapy.

Patients and methods

Patient selection and study design

Forty female outpatients (age, 20–80 years) with cervical cancer, staged IB to IVB based on the International Federation of Gynecology and Obstetrics (FIGO) staging system, initially underwent (chemo)-external beam radiotherapy prior to four fractions of brachytherapy from June 2013 to September 2014 were enrolled in the study on a voluntary basis.

The inclusion criteria were good consciousness, an ability to understand and provide information, no hearing impairment, and an Eastern Cooperative Oncology Group performance level of 0 to 2. The exclusion criteria were prior pelvic brachytherapy and a history of allergy to meperidine, fentanyl, or benzodiazepine. The measurement parameters were the numerical rating scale for pain score (0–10) and the EuroQol five-dimension questionnaire (EQ-5D) for QoL, given their reliabilities as previously demonstrated [14, 18, 19]. The patients were randomized into six groups. Each group received 10 mg of an intravenous benzodiazepine. These anesthetics were sealed in six paper bags by a nurse not involved in the study. The sample size of 40 patients was determined using a 10% difference in the visual numeric pain scale score (α = 0.05, β = 0.2). Using Stata version 12 (StataCorp, College Station, TX, USA), two-sample comparison of means revealed a required number of 73 patients in each group. Therefore, each patient was treated with 4 fractions of brachytherapy (80 fractions in each drug group), and the total number of patients was 40. Patients grouping and randomization followed the diagram (Fig. 1).

Brachytherapy procedures

Before the brachytherapy procedure, each patient was restricted to nothing by mouth (NPO) for 6 h, and a 22-G needle was cannulated in either forearm for intravenous fluid administration. The patient-reported pain score was assessed prior to the intervention and every 15 min throughout the procedure. QoL was assessed using the EuroQol five-dimension questionnaire (EQ-5D) before the treatment and immediately after completion of each fraction. Information regarding the drug used was blinded from both the patients and staff members directly involved in the procedure (radiation oncologists, nurses, radiotherapists, and medical physicists).

Sedation regimen and patient monitoring

All patients received supplemental oxygen via a cannula at 3 L/min. Percutaneous oxygen saturation, electrocardiography parameters, heart rate, and noninvasive blood pressure were monitored every 5 min. Each patient received four fractions of brachytherapy: either two fractions each of fentanyl and a benzodiazepine or two fractions each of meperidine and a benzodiazepine. Each drug was diluted with 10 mL of colorless normal saline in a clear syringe and labeled "protocol drug." Some syringes contained 50 mg of meperidine and others contained 100 mg of fentanyl. One of these two opioids was administered, followed by benzodiazepine after 1 min. An additional opioid at a dose determined by the radiation oncologist was administered if the pain score was ≥4. After the protocol, the patients were transferred to the recovery room for standard monitoring and care for 1 h.

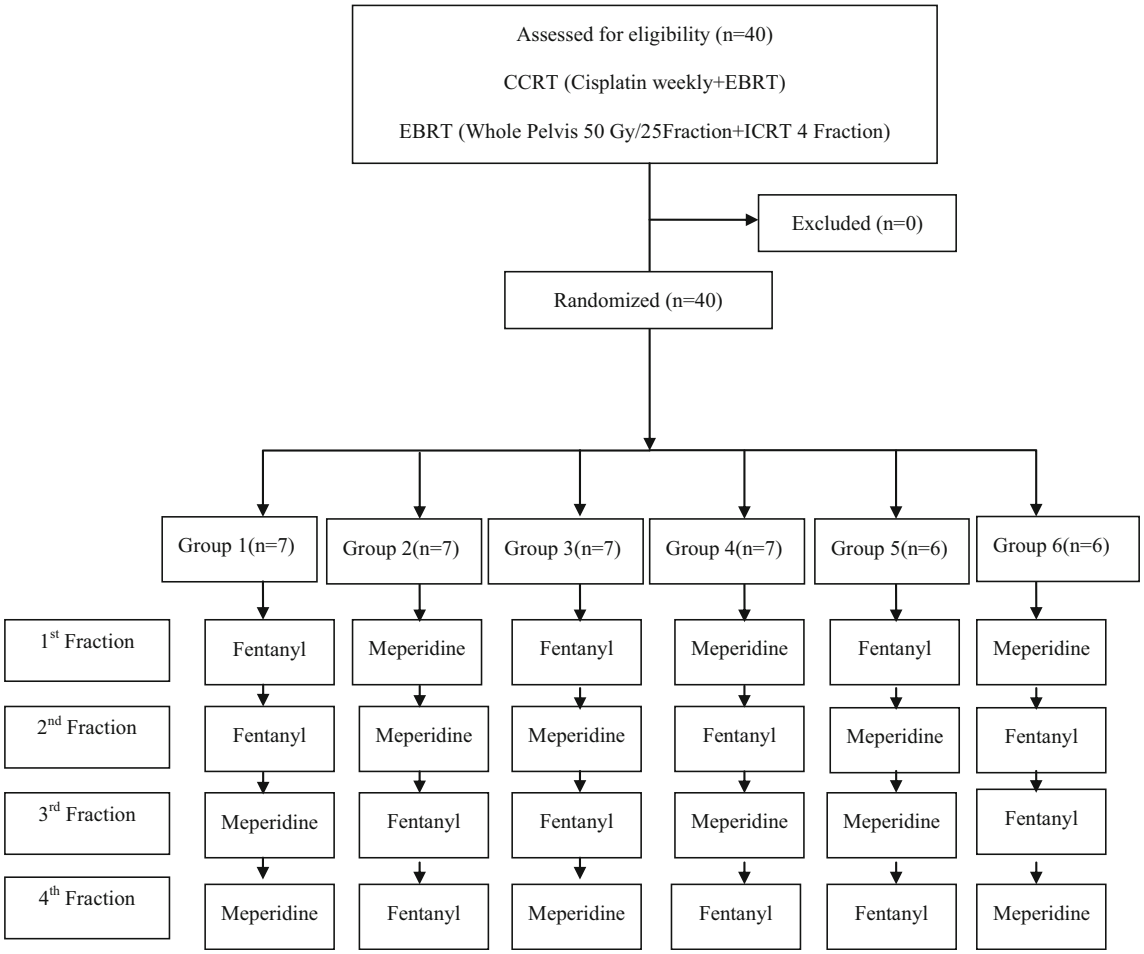


Fig. 1 Flowchart diagram of included patients. Patients were randomized into six different treatment groups for their orders of analgesics received

Data collection

The following data were collected: radiation treatment technique, tumor size, ovoid size, radiation dose, duration of brachytherapy treatment, applicator insertion time, and time in the recovery room.

Data analysis

The patients' demographic data are expressed as frequency and percentage. Parameters are expressed as mean and standard deviation. Categorical data were analyzed using the chi-square test, whereas the pain score and QoL were analyzed using Fisher's exact test. Comparisons between the two groups were examined by a non-dependent *t* test. All data were explored using Stata/SE version 12 (StataCorp). A p value of <0.05 was considered statistically significant and is presented with its 95% confidence interval.

Results

Forty patients with cervical cancer were enrolled in the study, and none were subsequently excluded. The median patient age was 56 years (range, 32–79 years). Most of the patients had stage IIb and IIIb cervical cancer, based on FIGO staging, accounting for 40.0 and 37.5%, respectively. Additionally, most of the patients (75.0%) received two-dimensional conformal brachytherapy. The patients' demographic data are presented in Table 1.

The average duration of the procedure was 2.5 ± 0.5 h. The median ovoid size was 2 cm, and the average tumor size and radiation dose were 2.0 ± 0.5 cm and 37.6 ± 15.6 cGy, respectively. The total dose of intravenous meperidine and fentanyl was 50.13 ± 0.26 mg and 100.18 ± 0.32 μg, respectively (Table 2). The duration of applicator insertion was 17.0 ± 7.53 and 20.31 ± 12.77 min for the patients treated with meperidine and fentanyl, respectively. During the insertion time, the patients experienced pain; however, the difference in pain severity between the two groups was not significant.

Table 1 Patient demographics. Age is presented as mean ± standard deviation; the remaining data are presented as number (percent) of patients ($N = 40$)

Age in years	56.7 ± 12.9
Radiation modality	
2D conformal	30 (75.0)
3D conformal	10 (25.0)
FIGO stage	
IB	5 (12.5)
IIA1	2 (5.0)
IIA2	1 (2.5)
IIB	16 (40.0)
IIIB	15 (37.5)
IVB	1 (2.5)

2D two-dimensional, *3D* three-dimensional, *FIGO* International Federation of Gynecology and Obstetrics

Following the randomization scheme which attempted to minimize inter-patient partiality on assessing the pain scores, we found that although there were no statistically significant differences in the pain scores between the two groups from baseline to discharge (Table 3), patients receiving fentanyl appeared to experience slightly more severe pain than those treated with meperidine, as shown in Fig. 2. At 45 min, the pain levels were peaked; it was likely due to the pressure in the bladder and vaginal cavity as the vaginal cavity was packed with gauze rolls to hold the bladder and rectum in place for fixed positioning before loading of the iridium source. The patients then received additional analgesics if their pain levels were 4 or above. Further, we assessed the patients' QoL using the EQ-5D questionnaire and found that their QoL was marginally affected by brachytherapy treatment (Table 4). Pain and discomfort were the main problems that the patients had to endure, followed by anxiety and depression. The two treatment groups also showed no significant differences among the five QoL dimensions. Finally, no significant cardiovascular or respiratory events occurred during the procedure.

Table 2 Treatment-related factors for each treatment group. Data for each brachytherapy fraction were recorded and presented as mean ± standard deviation

Variable	Meperidine ($n = 80$)	Fentanyl ($n = 80$)	p value
Ovoids size in cm, median (range)	2 (1.5–3)	2 (1.5–3)	1.000
Tumor size average (cm)	2.23 ± 1.29	2.21 ± 1.25	0.710
Tumor size at			
1st fraction	3.00 ± 1.13	3.20 ± 1.31	0.609
2nd fraction	2.35 ± 1.13	2.61 ± 1.15	0.474
3rd fraction	1.75 ± 1.12	2.10 ± 1.02	0.307
4th fraction	1.61 ± 1.02	1.32 ± 0.94	0.371
Drug dose	50.13 ± 0.26 (mg)	100.18 ± 0.32 (μg)	0.387
Applicator insertion time (min)	17.00 ± 7.53	20.31 ± 12.77	0.207
Radiation dose (Gy)	37.52 ± 15.17	38.41 ± 15.32	0.601

Table 3 Levels of pain score assessed from the patients starting from pre-procedure and every 15 min into the brachytherapy procedure. Pain score is scaled from 0 to 10. Data presented as mean ± standard deviation

Variable	Pain		p value[a]
	Meperidine($n = 80$)	Fentanyl ($n = 80$)	
Baseline	0.04 ± 0.25	0.14 ± 0.55	0.146
Min 0	0.49 ± 1.18	0.40 ± 1.16	0.328
Min 15	0.59 ± 1.38	0.65 ± 1.21	0.472
Min 30	1.05 ± 1.76	1.24 ± 2.21	0.915
Min 45	1.33 ± 2.09	1.70 ± 2.48	0.447
Min 60	0.61 ± 1.48	0.81 ± 1.83	0.524
Min 75	0.49 ± 0.99	0.53 ± 1.12	0.938
Min 90	0.24 ± 0.80	0.13 ± 0.58	0.160
Min 105	0.24 ± 0.80	0.13 ± 0.58	0.160
Discharge	0.24 ± 0.80	0.13 ± 0.58	0.160

[a] Mann–Whitney U test

Discussion

Patients undergoing intracavitary brachytherapy require insertion of an intrauterine tandem and vaginal colpostats, which can cause severe vaginal discomfort [15]. Conscious sedation is a preferred choice for brachytherapy as opposed to general anesthetic due to lower complication rates and shorter recovery time which allows applicability for outpatient setting [12, 20]. Several regional and alternative anesthetics have been introduced for the procedure [21]. Fentanyl has become an analgesic of choice because of its rapid onset and clearance [12], while intramuscular injection of meperidine has long been administered as part of the procedure. These two medications were previously compared in 70 patients undergoing closed reduction of fractures and dislocations, and there was no difference in the visual analog pain scores between patients receiving meperidine and those receiving fentanyl, both in combination with midazolam [22]. These results are consistent with our data, which showed no clear efficacy in pain relief during the brachytherapy procedure in either group, as tumor sizes were not statistically different between the groups. The patients received different sequences of the two analgesics in order to avoid varied treatment responses, tumor sizes, and individual pain perceptions which could cause biased in pain score assessment. Similarly, the two analgesics were equally effective in terms of sedation for pediatric

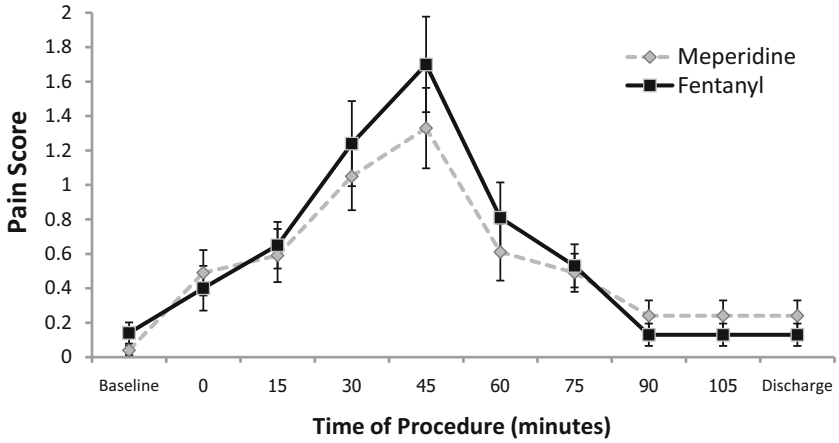


Fig. 2 Pain levels of patients undergoing intracavitary brachytherapy for cervical cancer at indicated time points during the procedure. Patients received benzodiazepine with either fentanyl or meperidine as anesthesia

gastrointestinal endoscopy [23]. However, a randomized controlled trial on the pain scores and procedure times of 111 patients undergoing gastrointestinal endoscopy showed that meperidine was associated with better pain scores while fentanyl was associated with a significantly shorter procedure time [24]. These findings were in accordance with a study of 1963 outpatients undergoing gastrointestinal endoscopy by Dzeletovic et al. [25].

During the treatment period, most patients experienced a moderate level of pain; this is consistent with the findings of many studies regardless of the analgesics used [12, 15, 22, 26]. One exception is a study of the effects of caudal epidural anesthesia during brachytherapy, which demonstrated moderately high pain scores ranging from 5.17 to 6.80 [27]. Our results further highlight that fact that although neither fentanyl nor meperidine showed distinct superiority over the other, we could decrease the patients' pain to very mild levels (score of 0.04–1.70) by re-administering the drugs, as needed, if the pain scores were 4 or above regardless of the step in the procedure as to minimalize the pain to be within the range of a mild level (score 1–3). The total treatment duration was also similar for both drugs, unlike in gastrointestinal endoscopy, because the dose rate of radiation determined the length of time.

With respect to QoL, both fentanyl and meperidine had undistinguished effects on the patients' daily activities and perceptions. This result is consistent with the findings of a previous study of 54 patients under sedation with propofol/fentanyl and midazolam/meperidine; the authors found no differences in the patients' pain scores or satisfaction [28]. Several studies on brachytherapy have emphasized patients' post-treatment QoL, including sexual function, vaginal changes, and menopausal symptoms [29, 30]. Conversely, the focus of the present study was the patients' day-to-day undertakings, for which neither drug showed superior efficacy. Nevertheless, previous reports have indicated that the mental health of patients with cervical cancer decreased a few years after the radiotherapy treatment. The patients' main concerns were body image and sexual concerns, and their QoL in the psychological domain sometimes plummeted even 15 years after the treatment [31–33]. An extended assessment of the patients' QoL could provide a broader comparison of the two medications.

The major limitations of this study are that it was based on a single-center design and that we did not measure the difficulty

Table 4 Quality of life of the patient assessed with the EQ-5D questionnaire. Data are presented as number (percent) of patients ($N = 40$, each underwent 4 separate procedures, totally 160 procedures)

Variable	Quality of life			*p* value[a]
	No problems	Some problems	Severe problems	
Mobility before treatment	31 (77.5)	9 (22.5)	0 (0.0)	
Mobility after treatment				
Meperidine	62 (78.5)	16 (20.2)	1 (1.3)	0.849
Fentanyl	58 (75.3)	18 (23.4)	1 (1.3)	
Self care before treatment	35 (87.5)	4 (10.0)	1 (2.5)	
Self care after treatment				
Meperidine	68 (86.1)	11 (13.9)	0 (0.0)	0.213
Fentanyl	69 (89.6)	6 (7.8)	2 (2.6)	
Usual activities before treatment	31 (77.5)	8 (20.0)	1 (2.5)	
Usual activities after treatment				
Meperidine	55 (69.6)	22 (27.8)	2 (2.5)	0.955
Fentanyl	53 (68.8)	21 (27.3)	3 (3.9)	
Pain/discomfort before treatment	20 (50.0)	20 (50.0)	0 (0.0)	
Pain/discomfort after treatment				
Meperidine	27 (34.2)	49 (62.0)	3 (3.8)	0.509
Fentanyl	23 (29.9)	53 (68.8)	1 (1.3)	
Anxiety/depression before treatment	26 (65.0)	14 (35.0)	0 (0.0)	
Anxiety/depression after treatment				
Meperidine	46 (58.2)	32 (40.5)	1 (1.3)	0.762
Fentanyl	42 (54.5)	33 (42.9)	2 (2.6)	

[a] Fisher's exact test

of applicator insertion. Additional research is needed to evaluate the difficulty of the procedure and factors influencing development of moderate to severe pain. Additional studies are also needed to develop nursing care and management protocols during brachytherapy by conscious sedation. The efficacy of nursing care interventions in multi-site studies needs to be tested and translated into practice to reduce pain and improve QoL for patients with cervical cancer receiving brachytherapy. Additionally, pain should be assessed every 15 min during the procedure because some patients may experience continuous pain. Overall, the present results suggest that outpatients with cervical cancer undergoing brachytherapy experience a moderate degree of pain. Given these data, the radiation oncologist and radiation oncology nurse should manage such patients to prevent their pain from becoming severe and assist them in transitioning to mild or no pain.

Based on the present and previous studies, meperidine and fentanyl appear to be safe and effective anesthetics for patients with cervical cancer. Repeated administration of these sedatives can also be performed to decrease the patients' pain levels and sustain their QoL. A long-term follow-up of their QoL and potential occurrences of posttraumatic stress disorder (PTSD) would be desirable to further evaluate their efficacies. According to the current study, as meperidine is relatively inexpensive compared with fentanyl and non-inferior pain-relieving efficacy, it has been regularly used by our radiation oncologists to relief pain in a conscious patient.

Acknowledgements This study was supported by Chulabhorn Hospital.

Compliance with ethical standards The study was approved by the Committee on Human Rights Related to Research Involving Human Subjects Chulabhorn Research Institute, number 20/2553. Written informed consent was obtained from all the patients.

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A (2015) Global cancer statistics, 2012. CA Cancer J Clin 65:87–108
2. Global Burden of Disease Cancer C, Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M et al (2015) The global burden of cancer 2013. JAMA Oncol 1:505–527
3. Siegel RL, Miller KD, Jemal A (2016) Cancer statistics, 2016. CA Cancer J Clin 66:7–30
4. Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM et al (2009) HPV screening for cervical cancer in rural India. N Engl J Med 360:1385–1394
5. Lukka H, Hirte H, Fyles A, Thomas G, Elit L, Johnston M et al (2002) Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer—a meta-analysis. Clin Oncol (R Coll Radiol) 14:203–212
6. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE et al (1999) Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 340:1137–1143
7. Waggoner SE (2003) Cervical cancer. Lancet 361:2217–2225
8. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA et al (1999) Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 340:1144–1153
9. Eifel PJ, Thoms WW Jr, Smith TL, Morris M, Oswald MJ (1994) The relationship between brachytherapy dose and outcome in patients with bulky endocervical tumors treated with radiation alone. Int J Radiat Oncol Biol Phys 28:113–118
10. Lanciano RM, Martz K, Coia LR, Hanks GE (1991) Tumor and treatment factors improving outcome in stage III-B cervix cancer. Int J Radiat Oncol Biol Phys 20:95–100
11. Kirchheiner K, Czajka-Pepl A, Ponocny-Seliger E, Scharbert G, Wetzel L, Nout RA et al (2014) Posttraumatic stress disorder after high-dose-rate brachytherapy for cervical cancer with 2 fractions in 1 application under spinal/epidural anesthesia: incidence and risk factors. Int J Radiat Oncol Biol Phys 89:260–267
12. Bhanabhai H, Samant R, E C, Grenier L, Lowry S (2013) Pain assessment during conscious sedation for cervical cancer high-dose-rate brachytherapy. Curr Oncol 20:e307–e310
13. Benrath J, Kozek-Langenecker S, Hupfl M, Lierz P, Gustorff B (2006) Anaesthesia for brachytherapy—51/2 yr of experience in 1622 procedures. Br J Anaesth 96:195–200
14. Smith MD, Todd JG, Symonds RP (2002) Analgesia for pelvic brachytherapy. Br J Anaesth 88:270–276
15. Chen HC, Leung SW, Wang CJ, Sun LM, Fang FM, Huang EY et al (1998) Local vaginal anesthesia during high-dose-rate intracavitary brachytherapy for cervical cancer. Int J Radiat Oncol Biol Phys 42:541–544
16. Nguyen TV, Petereit DG (1998) High-dose-rate brachytherapy for medically inoperable stage I endometrial cancer. Gynecol Oncol 71:196–203
17. Petereit DG, Sarkaria JN, Chappell RJ (1998) Perioperative morbidity and mortality of high-dose-rate gynecologic brachytherapy. Int J Radiat Oncol Biol Phys 42:1025–1031
18. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH et al (2011) Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manag 41:1073–1093
19. Sakthong P, Sonsa-Ardjit N, Sukarnjanaset P, Munpan W (2015) Psychometric properties of the EQ-5D-5L in Thai patients with chronic diseases. Qual Life Res 24:3015–3022
20. Lim KH, Lu JJ, Wynne CJ, Back MF, Mukherjee R, Razvi K et al (2004) A study of complications arising from different methods of anesthesia used in high-dose-rate brachytherapy for cervical cancer. Am J Clin Oncol 27:449–451
21. Watanabe Nemoto M, Nozaki-Taguchi N, Togasaki G, Kanazawa A, Kurokawa M, Harada R et al (2015) New approach to relieving pain and distress during high-dose-rate intracavitary irradiation for cervical cancer. Brachytherapy 14:642–647
22. Soysal S, Karcioglu O, Demircan A, Topacoglu H, Serinken M, Ozucelik N et al (2004) Comparison of meperidine plus midazolam and fentanyl plus midazolam in procedural sedation: a double-blind, randomized controlled trial. Adv Ther 21:312–321
23. Ali S, Davidson DL, Gremse DA (2004) Comparison of fentanyl versus meperidine for analgesia in pediatric gastrointestinal endoscopy. Dig Dis Sci 49:888–891
24. Robertson DJ, Jacobs DP, Mackenzie TA, Oringer JA, Rothstein RI (2009) Clinical trial: a randomized, study comparing meperidine (pethidine) and fentanyl in adult gastrointestinal endoscopy. Aliment Pharmacol Ther 29:817–823

25. Dzeletovic I, Harrison ME, Crowell MD, Ramirez FC, Yows CR, Harris LA et al (2013) Impact of fentanyl in lieu of meperidine on endoscopy unit efficiency: a prospective comparative study in patients undergoing EGD. Gastrointest Endosc 77:883–887
26. Rollison B, Strang P (1995) Pain, nausea and anxiety during intrauterine brachytherapy of cervical carcinomas. Support Care Cancer 3:205–207
27. Isoyama-Shirakawa Y, Nakamura K, Abe M, Kunitake N, Matsumoto K, Ohga S et al (2015) Caudal epidural anesthesia during intracavitary brachytherapy for cervical cancer. J Radiat Res 56:583–587
28. Agostoni M, Fanti L, Arcidiacono PG, Gemma M, Strini G, Torri G et al (2007) Midazolam and pethidine versus propofol and fentanyl patient controlled sedation/analgesia for upper gastrointestinal tract ultrasound endoscopy: a prospective randomized controlled trial. Dig Liver Dis 39:1024–1029
29. Ferrandina G, Mantegna G, Petrillo M, Fuoco G, Venditti L, Terzano S et al (2012) Quality of life and emotional distress in early stage and locally advanced cervical cancer patients: a prospective, longitudinal study. Gynecol Oncol 124:389–394
30. Jensen PT, Groenvold M, Klee MC, Thranov I, Petersen MA, Machin D (2003) Longitudinal study of sexual function and vaginal changes after radiotherapy for cervical cancer. Int J Radiat Oncol Biol Phys 56:937–949
31. Mirabeau-Beale KL, Viswanathan AN (2014) Quality of life (QOL) in women treated for gynecologic malignancies with radiation therapy: a literature review of patient-reported outcomes. Gynecol Oncol 134:403–409
32. Korfage IJ, Essink-Bot ML, Mols F, van de Poll-Franse L, Kruitwagen R, van Ballegooijen M (2009) Health-related quality of life in cervical cancer survivors: a population-based survey. Int J Radiat Oncol Biol Phys 73:1501–1509
33. Le Borgne G, Mercier M, Woronoff AS, Guizard AV, Abeilard E, Caravati-Jouvenceaux A et al (2013) Quality of life in long-term cervical cancer survivors: a population-based study. Gynecol Oncol 129:222–228