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CLINICAL RESEARCH

Propofol with or without fentanyl for pain relief after transrectal ultrasound-guided prostate (TRUS-P) biopsy: a randomized controlled study☆

Sirilak Suksompong, Panop Limratana *, Niruji Saengsomsuan, Nattaporn Wongsawang, Nophanan Chaikittisilpa

Mahidol University, Faculty of Medicine Siriraj Hospital, Department of Anesthesiology, Bangkok, Thailand

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Cancer of prostate;
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Abstract
Background: Postoperative pain from transrectal ultrasound-guided prostate (TRUS-P) biopsy under sedation is often mild. Benefit of opioids used during sedation is controversial.
Objective: The objective was to compare numeric rating scale (NRS) score at 30 minutes after TRUS-P biopsy between patients receiving propofol alone or with fentanyl.
Methods: We randomly allocated 124 patients undergoing TRUS-P biopsy to receive either fentanyl 0.5 mcg.kg^{-1} (Group F) or normal saline (Group C). Both groups received titrated propofol sedation via Target-controlled infusion (TCI) with Schneider model until the Observer's Assessment of Alertness/Sedation (OAA/S) scale 0–1 was achieved. Hemodynamic variables, patient movement, postoperative pain score, patient and surgeon satisfaction score were recorded.
Results: Overall, most patients (97.5%) had no to mild pain. Group F had significantly lower median NRS score at 30 minutes compared to Group C (0 [0, 0] vs. 0 [0, 0.25], $p = 0.039$). More patients in Group C experienced pain (90% vs. 75.8%, $p = 0.038$). Perioperative hypotension was higher in group F (81.7%) compared to Group C (61.3%) ($p = 0.013$). Thirty-five (56.5%) patients in Group F and 25 (42.7%) patients in Group C had movement during the procedure ($p = 0.240$). Surgeon's satisfaction score was higher in Group F (10 [9, 10]) than Group C (9 [9, 10]) ($p = 0.037$).
Conclusion: Combining low dose fentanyl with TCI propofol sedation may provide additional benefit on postoperative pain after TRUS-P biopsy, but results in perioperative hypotension. Fentanyl may attenuate patient movement during the procedure, which leads to greater surgeon's satisfaction.

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* Corresponding author.
E-mail: panop.lim@mahidol.ac.th (P. Limratana).

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Introduction

Transrectal ultrasound-guided prostate (TRUS-P) biopsy is a common minor urological procedure which unacceptable pain during this procedure was reported by 22–68% of the patients.[1,2] Pain and discomfort are usually caused by rectal probe insertion and 10–12 core needle biopsies. After the procedure, some of the patients may still feel uncomfortable with the gauze or cotton balls packing inside the rectum.

Various techniques have been used to alleviate pain during TRUS-P biopsy, for instance, intrarectal local anesthetics (IRLA), periprostatic nerve block (PNB), periprostatic infiltration of local anesthetic (PILA), low-dose spinal anesthesia, and intravenous mild to deep sedation.[3] Sedation has been reported to improve pain after the procedure and increase patient's satisfaction.[4,5] Several drug regimens and administration methods have been described, including midazolam and fentanyl (infusion),[5] propofol alone (intravenous bolus),[6] propofol (target-controlled infusion; TCI) and remifentanil,[4] propofol (intravenous bolus) and fentanyl,[6] and propofol and ketamine (ketofol) (intravenous bolus).[7]

Barbosa et al.[6] compared between propofol alone (intravenous bolus) and propofol with low dose fentanyl and reported incidence of moderate to severe postoperative pain were much higher in the group without fentanyl (40% vs. 7%, respectively). On the other hand, Park et al.[8] studied on TCI propofol sedation and reported that patients sedated with TCI propofol alone until either no response to noxious stimuli or mild padding during the procedure was achieved, had low postoperative pain score (mean pain score of 1.4) and high satisfaction score. It is well-demonstrated from these previous studies that deep sedation can reduced pain and discomfort during and after TRUS-P, however, the benefit of adjunct fentanyl to deep propofol sedation is controversial.

The primary objective of this study was to compare the intensity of immediate postoperative pain after TRUS-P biopsy between propofol alone or combined propofol and fentanyl. We also compared the incidence of pain, adverse events, and satisfaction.

Methods

This was a prospective randomized, double-blinded, parallel group, placebo-controlled study. This single-center study was conducted in a 2,500-bed tertiary care university hospital in Bangkok, Thailand. This phase IV study was designed as a superiority study because we hypothesized that adjunct fentanyl could be helpful in alleviate pain after the procedure. The study was approved by the Institutional Review Board (IRB number Si 106/2016) (Appendix 1) and was registered in ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT02733705) prior to patient recruitment.

Informed consent was obtained from all patients. Patients aged over 18 years with American Society of Anesthesiologists physical status (ASA) classification I–III and BMI < 30 $kg.m^{-2}$ who were scheduled for TRUS-P biopsy were included in this study. Exclusion criteria were patients with a history of allergy to the study drugs or drugs dependence, abnormal coagulogram or unable to cooperate. Randomization (block of 4) was computer-generated. The allocation assignments were put into sealed envelopes with running numbers 1 to 124. The patients were equally randomized into two groups (1:1); Group F (propofol and fentanyl) and Group C (propofol and normal saline). Both groups received propofol infusion using a target-controlled infusion (TCI) with Schneider model[9] (Fresinius Kabi, Injectomat TIVA Agilia®). In Group F, the patients received 0.1 $mL.kg^{-1}$ of fentanyl (5 mcg. mL^{-1} in 10 mL syringe), while Group C received 0.1 $mL.kg^{-1}$ of placebo (normal saline in 10 mL syringe). The study drugs were prepared by anesthesia personnel who did not involve in the anesthesia care and normal saline was used as placebo. The caregivers and the outcome assessors were blinded to the patient's group.

Upon arrival to the operating theater, routine standard monitoring (noninvasive blood pressure – NIBP, electrocardiogram, pulse oximetry and respiratory rate) was placed and oxygen supplementation was given via nasal cannula 3 $L.min^{-1}$. The study drug was administered 0.1 $mL.kg^{-1}$ bolus prior to propofol infusion. Propofol was administered using target-controlled infusion (Schneider model)[9] started with the target of effect-site concentration (Cet) at 2.5 mcg. mL^{-1} and incrementally increased by 0.1 mcg. mL^{-1} until the observer's assessment of alertness/sedation (OAA/S)[10] scale 0–1 was achieved before incision. The OAS/S was graded as follows: 0, no respond to painful trapezius squeeze; 1, respond only after painful trapezius squeeze; 3, respond only after mild prodding or shaking; 4, respond lethargically to name spoken in normal tone lethargic; and 5, respond readily to name spoken in normal tone. During the procedure, patient movements were evaluated to determine the quality of sedation and were graded as: 1, no movement; 2, minor movement not interfering with the procedure; 3, purposeful movement transiently interfering with the procedure; 4, purposeful movement that made the procedure difficult; and 5, requirement for supplementation with general anesthesia to complete the procedure.

At the end of the procedure, the surgeons were asked to evaluate a 10-point satisfaction score. After the procedure, the patients were transferred to the postanesthesia care unit (PACU) where postoperative NRS score (0 = no pain, 10 = the worst imaginable pain), hemodynamic variables, Aldrete score, nausea and vomiting, urinary catheterization, hematuria, bleeding per rectum, fever, and patient's satisfaction were evaluated. We also calculated the total cost of sedation included propofol, fentanyl ephedrine, atropine, nasopharyngeal airway, TCI machine, and medications given in the postanesthesia care unit. The cost of propofol was calculated per ampule not per milliliter of drug.

Statistical analysis

In this study, it was anticipated that there would be a difference in mean NRS score within 30 minutes after procedure between fentanyl and NSS group. A previous study in the propofol group revealed mean pain score before discharge from postanesthesia care unit was 0.9 (standard deviation [SD] = 1.1).[8] Using the difference of 0.5, SD of 1.1, type I

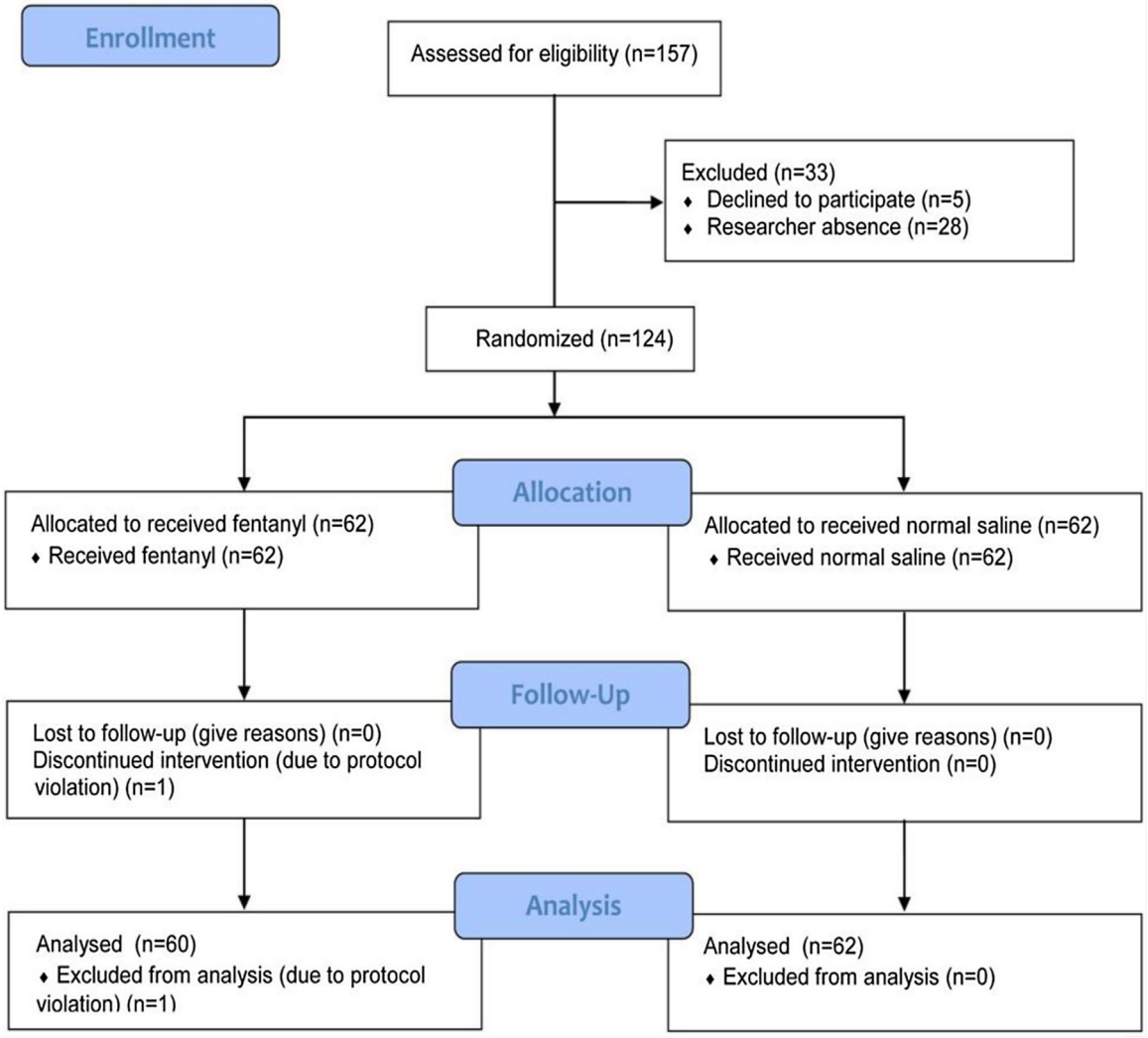

Figure 1 CONSORT flow of the included patients.

error of 0.05 and 80% power, a sample of 61 patients per group was calculated.

Data were analyzed using Predictive Analytics Software Statistics 18.0.0 (Chicago, IL, USA, SPSS Inc.). Continuous data such as age, body mass index (BMI), NRS score, target of effect-site concentration (Cet), and time to achieved (OAA/S) scale 0–1 are presented as mean ± SD or median (P_{25}, P_{75}) and compared using the Student *t*-test or Mann-Whitney U test.

Categorical data such as gender, ASA and incidence of side effects are presented as number (percentage) and were compared using the chi-square test. A *p*-value less than 0.05 was considered statistically significant.

Results

From January 2017 to May 2018, 157 patients scheduled for TRUS-P biopsy were screened for eligibility criteria. Of these, 5 patients refused to participate and the research team was not available in 28 patients. As a result, a total of 124 patients were included in the study. In Group F, one patient had repetitive purposeful movements, so the investigator had to terminate the protocol and one other patient was excluded due to protocol violation (Figure 1). Finally, 60 patients in Group F and 62 patients in Group C were included in the final analyses. Demographic data for both groups are presented in Table 1. There were no significant differences in demographic and perioperative data between the two groups.

The median (P_{25}, P_{75}) NRS pain score at 30 minutes after TRUS-P biopsy in Group F was significantly lower than Group C (0 [0, 0]) vs. 0 [0, 0.25], $p = 0.039$). At 30 minutes, pain was reported by 6 (10.0%) patients in Group F compared to 15 (24.2%) patients in Group C ($p = 0.038$). One patient (1.7%) in Group F reported severe pain (NRS = 8), while two patients (3.2%) in Group C (NRS = 7), in which, all required narcotics for pain treatment (Figure 2).

The mean propofol dosage were significantly lower in Group F (137.5 ± 44.6 mg) compared to Group C (161.4 ± 43.0 mg) ($p = 0.003$). The median [P_{25}, P_{75}] of maximum Cet to achieve OAA/S of 0–1 for the procedure was also lower in Group F (2.8, [2.6, 3.1]) compared to Group C (3.1 [2.9, 3.3]) ($p = 0.0003$) (Figure 3). However, the incidence of hypotension was also higher in Group F

Table 1 Patient characteristics and perioperative data.

	Group F (n = 60)	Group C (n = 62)
Age (yr)	69.1 (7.3)	68.2 (8.5)
BMI (kg.m^{-2})	24.0 (3.4)	24.6 (3.0)
ASA I:II:III	1 (1.7): 43 (71.7): 16 (26.7)	5 (8.1):45 (72.6): 12 (19.4)
Anesthetic time (min)	15.2 (5.9)	16.4 (5.1)
Operation time (min)	8.3 (3.7)	8.6 (3.2)
Time to OAA/S 0–1 (min)	6.3 (4.0)	7.2 (2.7)
Bleeding per rectum	2 (3.3)	2 (3.2)
Packing gauze/cotton ball	57 (95.0)	59 (95.2)
No. of core needle biopsy	12.7 (2.2)	12.5 (2.2)
Urinary catheter		
No	39 (65.0)	44 (71.0)
Yes, intermittent after the procedure	1 (1.7)	2 (3.2)
Yes, retained	20 (33.3)	16 (25.8)

ASA, American Society of Anesthesiologists physical status; OAA/S; Observer's Assessment of Alertness/Sedation Scale.
Data are present as mean (SD) or number of patients (%).

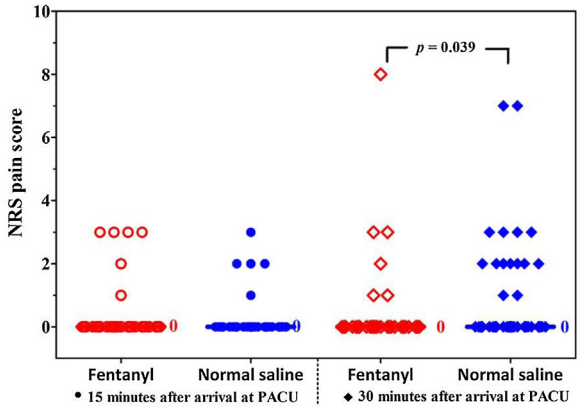

Figure 2 Distribution and median numeric rating scale (NRS) pain score of Group F (red) and Group C (blue) at 15 and 30 minutes after arrival at postanesthesia care unit (PACU).

(81.7%) compared to Group C (61.3%) (p = 0.013) (Table 2). The incidence of movement that interfere with the procedure were slightly higher in Group C (25.8%) in compared to Group F (16.7%), however, no statistical significance was demonstrated (p = 0.240) (Table 2).

There was no significant difference in patient's satisfaction score in groups F (10 [10, 10]) and C (10 [10, 10]) (p = 0.780), whereas surgeon's satisfaction score was significantly higher in Group F (10 [9, 10]) than Group C (9 [9, 10])) (p = 0.037). There was also no difference in hypoxia and bradycardia between the two groups. The average anesthesia cost of per patient in Group C (US$ 11.8) was US$ 1.9 higher than Group F (US$ 9.9).

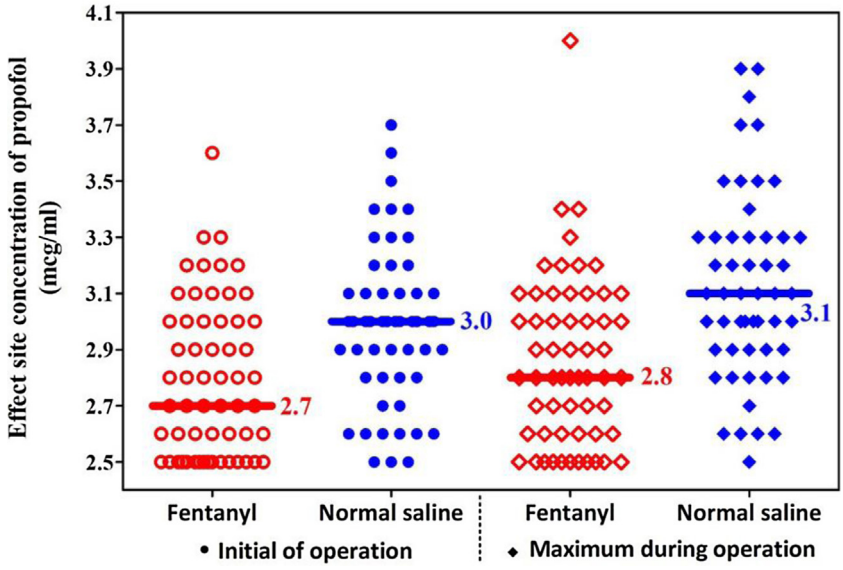

Figure 3 Distribution and median of effect site concentration of propofol (Cet) among Group F (red) and Group C (blue) at start and at maximum concentration.

Table 2 Incidence of perioperative complications.

	Group F (n = 60)	Group C (n = 62)	*p*-value
Hypoxia			0.550
Arouse	0 (0)	1 (1.6)	
Airway management	4 (6.7)	3 (4.8)	
Nasopharyngeal airway	1 (1.7)	3 (4.8)	
Hypotension	49 (81.7)	38 (61.3)	0.013
Bradycardia required intravenous atropine	1 (1.7)	1 (1.6)	0.981
Movement during the procedure			0.240
No movement	35 (58.3)	27 (43.5)	
Not interfere with procedure	15 (25.0)	19 (30.6)	
Interfere with procedure	10 (16.7)	16 (25.8)	

Data are present as number of patients (%).

Discussion

The main findings of this study are that 1) target-controlled infusion of propofol can be used as a sedation technique for TRUS-P biopsy to reduce pain and discomfort, 2) despite no to mild immediate postoperative pain was mostly observed in both groups, adjunct low-dose fentanyl further reduce pain, 3) fentanyl also decreases TCI propofol dosage and patient's movement interfering the procedure but results in a higher incidence of hypotension, and 4) overall high patient's and surgeon's satisfaction can be achieved using TCI propofol sedation, however, surgeon's satisfaction is higher in fentanyl group.

Postoperative pain after TRUS-P biopsy

Although some previous papers had demonstrated high incidence of pain and pain score during TRUS-P biopsy, only no to mild pain was reported in studies using intravenous sedation. The incidence of moderate to severe pain for TRUS-P biopsy using propofol alone were 7–40%,[6,11,12] and only 0–7% when combined with opioids.[4,6,12,13] Overall, average pain score from previous studies were 0–3, with or without opioids.[4,6,11,14] In our study, 17.2% of the patients in both groups had experienced any pain in PACU and among them, only 3 patients reported severe pain. The findings from previous studies and ours demonstrated that intravenous sedation using propofol with or without opioids was an effective method to reduce pain from TRUS-P biopsy and resulted in no to mild pain in most patients.

Our study demonstrated that adding low-dose fentanyl to TCI propofol sedation can reduce both the postoperative pain score and the incidence of postoperative pain 30 minutes after TRUS-P biopsy. These results were consistent with previous studies, which combined the use of opioids with propofol for sedation in TRUS-P biopsy. Seo et al.[12] reported that adding 0.5 $mg.kg^{-1}$ meperidine to propofol sedation resulted in less average postoperative pain compared to control (Mean NRS pain score of 1.5 ± 1.9 vs. 0.4 ± 1.0, $p = 0.012$). Nichikawa et al.[13] compared fentanyl with propofol sedation with spinal anesthesia for TRUS-P biopsy. They reported no to mild pain in all patients during PACU stay in both groups and no significant difference was found in the incidence of mild pain in fentanyl/propofol group (25%) compared to spinal anesthesia (20%). Barbosa et al.[6] also demonstrated that patients receiving propofol with either 0.5 $mcg.kg^{-1}$ fentanyl had significantly lower pain at 15 and 60 minutes and required less pain killer after the procedure compared to those who received propofol alone. Postoperative pain score among patients undergoing TRUS-P biopsy in all studies is already low, however, our data demonstrated that approximately 20% of the patients still experienced pain. Further reduction in pain with low dose fentanyl may provide clinical benefit in some patients.

Hypotension

In this study, the incidence of perioperative hypotension required treatment was higher in patients receiving fentanyl (81.7%) compared to the control group (61.3%), which were higher than previous studies. In contrast to our study, Nishikawa et al.[13] found that 47.5% of the patients receiving fentanyl 1 $mcg.kg^{-1}$ together with propofol infusion experienced hypotension Meanwhile, in other studies, the incidence of hypotension in patients receiving only propofol were 40–48.6%, which was also lower than both groups in our study (61.3%). Propofol was given by bolus and followed either by infusion[15] or incremental bolus,[7,8] unfortunately, the total dose of propofol was not reported. The higher incidence of hypotension in our study compared to others might be due to the fact that we used propofol infusion guided by TCI model, which generally, result in higher amount of propofol dose in a shorter duration than the dose used in other studies.

Park et al.[8] also used TCI infusion of propofol for sedation in TRUS-P biopsy and reported no hypotension in their study. Unlike our study, the authors gradually titrated Cet of propofol until desirable level of sedation was achieved. They reported the mean Cet of 2.1 ± 0.3 $mcg.mL^{-1}$ was used to achieve a similar level of sedation to our study (OAA/S 0–1), which was lower than initial Cet setting of our study (Cet 2.5 $mcg.mL^{-1}$). The greater rate of hypotension in our study was likely due to higher Cet setting. Moreover, we did not include a protocol for Cet reduction when the patients developed hypotension. Thus, the incidence of hypotension may be reduced by starting with a lower Cet setting and then titrating to the target level of sedation.

However, the total sedation time was much longer although the procedural time was even shorter compared to

our study. Interestingly, combining propofol with fentanyl resulted in significantly higher incidence of hypotension despite smaller amount of total propofol given and lower Cet setting at the start of the procedure. On the other hand, previous studies demonstrated no significant difference in blood pressure profile among both patients receiving propofol alone either with 0.5 mcg.kg^{-1} fentanyl[6,7] or 0.5 mg.kg^{-1} meperidine.[12,14] Many studies comparing the use of propofol alone and combined with fentanyl for procedural sedation suggested that adding fentanyl could reduce propofol requirements without significant difference on blood pressure.[16–18] Similar to previous studies, the total dose of propofol was lower in the fentanyl group, however, the dose difference in our study was small and may have only little clinical significance. This may be due to the fact that we did not have a protocol for step down in Cet setting when blood pressure decreased.

Therefore, additional small dose of fentanyl could cause hypotension. The results suggested that TCI of propofol is a comparable option for TRUS-P biopsy sedation either alone or combined with fentanyl. The initial Cet of 2.5 mcg. mL^{-1} may be used for short induction time but should be decreased once blood pressure starts to decline to avoid hypotension. If opioid was given in addition to propofol, start with lower Cet and dose reduction early to prevent adverse hemodynamic effects.

Satisfaction

Patients' satisfaction scores for both groups in our study were high and not different between the two groups. Several studies had also showed similar results.[4,8,13,15,19] Although the overall cost is higher, the results were consistent among studies that patients receiving sedation with propofol had higher satisfaction score than those receiving local or topical analgesia.[4] Pain, even mild degree, is the main influencer on patient's satisfaction score. We did a further analysis and found that patients who had any level of pain demonstrated significantly lower satisfaction score than those without pain (10 [9, 10] vs. 10 [10, 10], $p = 0.029$). As a result, measures to alleviate pain should be considered to improve patient's satisfaction.

Surgeons' satisfaction score was higher in the fentanyl group. This is related to the frequency of patient movement during the procedure. Patient movement not only delays the surgery but may also be harmful to the patient and can disturb quality of tissue biopsy. In the previous study by Abdellatif et al.[7] reported a significantly better surgical condition in patients undergoing TRUS-P biopsy under ketofol (combined ketamine and propofol) compared to propofol alone. Another study by Sundarathiti et al.[15] also reported 100% vs. 57% of no movement during surgery using selective spinal anesthesia and propofol sedation, respectively.

Although we could not demonstrate a significant difference in movement between the two groups, the group receiving fentanyl seemed to have lower incidence of patient movement, especially the movement that interfere with the procedure. The results suggested that pain may be the primary reason for the patient to move during the procedure, therefore, adding low dose fentanyl may facilitate surgical condition.

Further study

Since most of the patients experienced no to mild pain, preoperative slow release oral paracetamol, especially 650 mg, which last 8 hours, may be a cost-effective alternative pain treatment for this procedure.

Limitations

The limitations in this study are no Bispectral index (BIS) monitoring and the protocol in this study did not provide a decrease in Cet during the study. Therefore, this may cause the higher incidence of hypotension.

Conclusion

In summary, combining low dose fentanyl with TCI propofol sedation may provide additional benefit on postoperative pain after TRUS-P biopsy, but results in higher incidence of perioperative hypotension. Fentanyl may attenuate patient movement during the procedure, which leads to greater surgeon's satisfaction.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjane.2021.02.001.

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