Research Article

Effects of fentanyl on procedural pain and discomfort associated with central venous catheter insertion: A prospective, randomized, double-blind, placebo controlled trial

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Abstract

Context: Central venous catheter (CVC) insertion induces pain and discomfort to a conscious patient despite application of a local anesthetic (LA) field block and this pain can be greatly lessened by using additional analgesics. **Aim:** The aim of this study is to evaluate the efficacy of fentanyl along with LA field infiltration in controlling pain and discomfort associated with CVC insertion. **Settings and Design:** A prospective, randomized, double-blind, placebo-controlled trial was conducted at tertiary referral center. **Materials and Methods:** Fifty-four patients scheduled for planned CVC were randomly assigned to receive either fentanyl (2 μg/kg) or 0.9% normal saline. Pain and discomfort using a verbal numeric rating pain scale at 5 times points during CVC insertion were assessed and analyzed. **Results:** The median interquartile range pain score is worst for placebo group after LAI (5 [3-6]) and in the immediate postprocedure period (5 [4-5]) which was significantly attenuated by addition of fentanyl (3.5 [2-5] and 3 [2-4]) (P = 0.009 and 0.001 respectively). Overall, fentanyl and placebo group were not statistically different with median discomfort score except at T10 (P = 0.047). **Conclusions:** Preprocedural bolus fentanyl infusion provides adequate analgesia and can be safely used for alleviating pain during CVC insertion in conscious patients.

Keywords: Analgesia, central venous catheter, fentanyl, procedural pain

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.136069

Quick Response Code:

Introduction

Central venous catheterization (CVC) is a frequently performed clinical procedure associated with pain, anxiety and discomfort.[1] Various methods have been investigated to alleviate pain due to CVC. Lignocaine infiltration at the point of insertion being the most commonly used technique to alleviate such pain. However, field block with subcutaneous local anesthetics (LA) induces considerable degree of pain.[2] Moreover, our experience suggest that in a conscious patient, even after the establishment of an effective field block, other subsequent procedural steps such as positioning (placing a rolled up towel between the scapulae to extend the head and patient was given 15-20° Trendelenberg position with the neck fully turned to the opposite side side) for CVC and anchoring the catheter to skin with suture may be associated with pain and discomfort. Ensuring adequate analgesia and sedation is therefore essential for patient comfort and satisfaction.

Many different types of analgesics can be added to prevent and/or control procedural pain. Yet, only very few investigators have examined the effect of additional analgesic usage, along with LA infiltration on pain associated with the procedure.

The use of short acting potent opioids such as fentanyl, administered intravenously (IV) as a bolus could

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alleviate such pain in a simple and effective manner by blocking the activity of central opiate receptors, whereas LA agents block pain transmission by interfering with nerve cell depolarization of peripheral pain fibers.

The purpose of this randomized prospective double-blind clinical trial was to evaluate objectively whether a single bolus dose of IV fentanyl before the procedure could prevent pain and discomfort during CVC.

Materials and Methods

After obtaining approval from the hospital ethics committee, 54 consecutive adult patients requiring central venous access with planned placement in the internal jugular vein (IJV) as a part of normal care were consented and enrolled in the study. No systemic analgesics had been administered for at least 4 h before the procedure.

Patients were included in this study if they were awake, alert, and oriented and their medical condition was stable enough to allow them to understand and use verbal numeric rating pain scale (VNRPS 0-10) and were 18 years or older. Patients were excluded from the study if they were receiving neuromuscular blocking medications or had a disease or injury that impaired sensory transmission proximal to the procedure site.

Ten minutes before the procedure, patients were allocated randomly to one of the two groups using a computer-generated random number table. An anesthetist, who was not one of the observers, prepared syringes containing either fentanyl 2 μg kg^{-1} (fentanyl group) or 0.9% saline (placebo group), all made to a total volume of 10 mL. All the solutions were labeled "study drug" and coded to maintain the double-blind nature of the study. The study drugs were infused to the patients as per their group allocation over 10 min using a syringe infusion pump.

The procedure commenced at the end of infusion of the study drugs. Each patient was to receive subcutaneous infiltration of 5 mL of 2% lidocaine after confirming the anatomical landmark of the target jugular vein using anterior approach.[3] The operator then injected 3 mL of the LA solution through a 25-gauge needle directly superficial to the IJV at the designated puncture site. This injection was given slowly over 5-10 s. The needle was then repositioned to inject additional LA, 1 mL just to the left and 1 mL just to the right of the vein for anchoring stitches. All the CVC were performed by a single investigator (first author).

Scores for discomfort, pain, sedation, cardiovascular event, respiratory events and peripheral oxygen saturation were recorded at rest by an anesthesia resident at 5 times points: Time 1, at base line (T1); Time 2, after initial LA injection (LAI) (T2); Time 3, immediately after the procedure, the patient was asked to report the peak pain experienced during the procedure (T3); Time 4, 10 min after completion of the procedure (T10) and Time 5, 60 min after completion of the procedure (T60). Patients were also closely monitored for any adverse effects of opioid such as respiratory depression, nausea, vomiting and pruritus.

Discomfort was assessed using a 11-point verbal numeric rating discomfort scale (VNRDS) from 0 to 10 (0: None, 10: Extreme discomfort); pain was assessed by a verbal numeric rating pain scale (VNRPS) from 0 to 10 (0: No pain, 10: The worst pain imaginable).[4] Both the scale was explained to each patient by the investigator, while counseling the patient regarding the need for central venous access, before the start of infusion of study drugs. Sedation was assessed on a six-point modified observer's assessment of alertness/sedation scale (OAA/S) with 0: No response and 6: Agitated.[5] If OAA/S score was 0 or 1 (patient un-arousable), VNRPS and VNRDS were counted as 0 (no pain and no discomfort).

Respiratory events were defined as SpO_2 <92% and/or respiratory rate (RR) <8 breaths/min. A decrease in SpO_2 to <92%for >30 s was treated sequentially with verbal stimulation, head tilt-chin lift, Guedel airway, and bag-mask-assisted ventilation. A RR < 8 breaths/min was treated sequentially with verbal stimulation, mild prodding, and nasopharyngeal stimulation. Cardiovascular events were defined as a single episode of variation in heart rate (HR) and systolic blood pressure (SBP) by >20% from patient baseline. Persistent (two reading 3 min apart) or recurrent SBP <90 mmHg, was treated with boluses of IV ephedrine 6 mg and/or persistent (>30 s) or recurrent HR <50 beats/min was treated with IV atropine 600 mcg.

Each patient received 7 Fr triple-lumen catheters via a nontunneled approach in the right IJV using anterior approach.[3]

Previous research suggests that a difference of 2.0-points on an 11-point VAS indicates a clinically important effect.[6] With this in mind, we calculated our sample size based on a previously reported pain scores of 3.6 (standard deviation [SD] 2.3) on 0-10 VAS during CVC using remifentanil infusion.[7] A reduction in pain

scores by two-point decrease on VNRPS was considered as acceptable. Twenty-four patients were required in each group, for an alpha-error of 0.05 and beta-error of 0.80. We randomized and recruited 27 patients in each group to allow for withdrawals.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc. (1999). SPSS 10.0 for Windows . SPSS Inc., Chicago IL.). Data are expressed as means (SD), medians (inter quartile ranges), or numbers, as appropriate. Unpaired Student's *t*-test (two tailed) for equal variance was employed for comparison of demography, baseline hemodynamic and respiratory data; Chi-square and Fisher's exact tests were employed to compare gender distribution and differences between predefined adverse effects in the groups. Pain, discomfort, and sedation score were analyzed using the Mann–Whitney rank sum test. Statistical significance was accepted at values <0.05.

Results

Fifty-four patients were recruited, with all but three completing the study. One patient from fentanyl group and two from placebo group were withdrawn due to a failure in identifying a patent jugular vein and the operator opted to cannulate the subclavian vein instead of the IJV.

There were no significant differences between the study group of patients in terms of demographics, baseline respiratory, cardiovascular parameters, and level of consciousness [Table 1].

The indications for CVC were difficulty in peripheral venous access/parenteral nutrition/infusion of caustic drugs, similarly distributed between the groups, that is, 11/10/5 in fentanyl and 14/6/5 in placebo group respectively [Table 1].

The median pain scores discomfort score and sedation score in fentanyl and placebo group are given in Figures 1-3 respectively. Comparison between groups revealed that placebo group had worst pain scores after LAI, which was significantly attenuated by addition of study drugs in fentanyl group (P = 0.009). Similarly, for subsequent procedural steps (T3, T10 and T60) fentanyl group had a lower pain score compared with placebo, but reached significance level only for T3 and T10 steps. However, the procedure related discomfort was comparable between the groups for all procedural steps except for T10 (10 min after the procedure).

The patients from fentanyl group tend to be more sedated (low mean sedation score), but most of the patients from either group were responding to verbal command. Two patients from fentanyl group need to be called repeatedly with mild prodding (OAA/S score-2) to ascertain level of sedation 10 min after the procedure (T10). The median sedation score for fentanyl group was significantly less in the immediate postprocedure period (T10) compared to placebo group, but for the rest of the time points we did not find a significant difference in median sedation score between the study groups [Figure 3].

Fentanyl group had a lower HR values than placebo at LAI and at the end of procedure but the difference is not

Table 1: Demographic data, base line variables and indications for CVC in patients receiving fentanyl or placebo

Variable	Fentanyl (n=26)	Placebo (n=25)	P value
Age (years)	42 (38-55)	46 (39-60)	0.447
Weight (kg)	50 (45-56)	50 (48-60)	0.639
Heart rate (bpm)	95 (78-110)	88 (78-100)	0.189
SBP (mmHg)	119 (109-132)	115 (109-135)	0.910
SpO_2 (%)	100 (100-100)	99 (98-100)	0.113
RR	18 (15-18)	18 (16-19)	0.719
Indications for CVC			
Caustic drugs			0.509
Metabolic acidosis	2	1	
Gastrointestinal malignancy	3	4	
Total parenteral nutrition			
Acute pancreatitis	6	4	
Entero-cutaneous fistula	3	2	
Radiation enteritis	1	0	
Venous access			
Burns	2	2	
Failed peripheral venous access	9	12	

Values are medians (IQR ranges 25-75) or numbers (n). bpm: Beats per minute; SBP: Systolic blood pressure; RR: Respiratory rate; SpO_2: Oxy-hemoglobin saturation by pulse oximeter; CVC: Central venous catheterization; IQR: Interquartile range

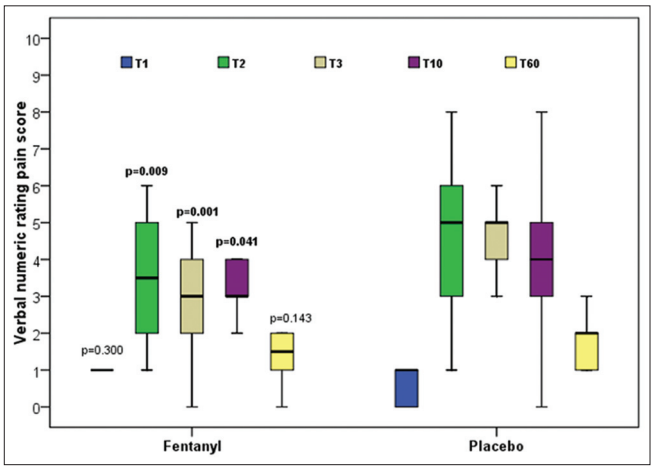

Figure 1: Comparison of pain score: Fentanyl versus placebo. T1: At base line; T2: After initial local anesthetic injection; T3: Immediately after the procedure, the patient was asked to report the peak pain experienced during the procedure; T10: 10 minutes after completion of the procedure; T60: 60 minutes after completion of the procedure, P<0.05 consider significant in comparison to placebo group

statistically significant. HR decreased by >20% of baseline in four and one patients from fentanyl and placebo group respectively. However, only one patient from fentanyl group experienced bradycardia requiring treatment as per predefined protocol. SBP decreased by >20% of baseline in a similar number of patients from both groups (one each).

More patients from fentanyl group (4/26) experienced episodes of SpO_2 < 92%, compared with placebo group (0/25), but the difference did not reach statistical significance [Table 2].

Two patients from fentanyl group complained of nausea. No patient vomited or required antiemetic medication. One patients from fentanyl group experienced transient pruritus.

Discussion

Central venous catheterization is one of the most commonly performed invasive procedures in intensive care unit (ICU) and is a source of pain and anxiety to the conscious patient and this pain is often reduced with the use of LAs.

For our study, we have defined pain as an unpleasant sensory and emotional experience that arises from actual or potential tissue damage associated with CVC. The sensory and emotional component of pain was assessed with VNRPS and VNRDS respectively.

The primary finding of the study are field infiltration with LA for CVC induces considerable degree of pain in conscious patients and fentanyl infusion can attenuate this and subsequent pain response significantly if given before such invasive procedure. Fentanyl group patients had a distinctly better pain score for all procedural steps except for base line (T1) and 60 min after the procedure (T60). Overall, fentanyl and placebo group were not statistically different with median discomfort score except in the immediate postprocedure period; however fentanyl group patients trended towards less discomfort score at 2 times points (T3 and T10).

Literature search revealed two studies,[1,8] describing pain and discomfort as two separate perception experienced by patients during CVC. Morrison *et al*.[1] in their five-point numeric rating scale described CVC as a moderately painful and severely uncomfortable procedure.

Puntillo *et al*.[9] demonstrated a big positive surge in mean pain intensity score at the time of CVC than the base line preprocedural pain. In their analysis, they found that, only 20% of patients received opioids

Table 2: Comparison of adverse effects and number of needle passes for successful cannulation in patients receiving fentanyl or placebo

Adverse event	Fentanyl (*n*=26)	Placebo (*n*=25)	*P* values
Hypotension (*n*)	1	2	0.031
Bradycardia (*n*)	4	1	0.049
Desaturation (*n*)*	4	0	0.055
Nausea (*n*)	2	0	0.343
Pruritus (*n*)	1	0	1.000
Number of needle passes (mean±SD)	1.2±0.5	1.1±0.3	0.229

Values are number of patients (0). *SpO_2<92% by peripheral pulse oximetry. SD: Standard deviation

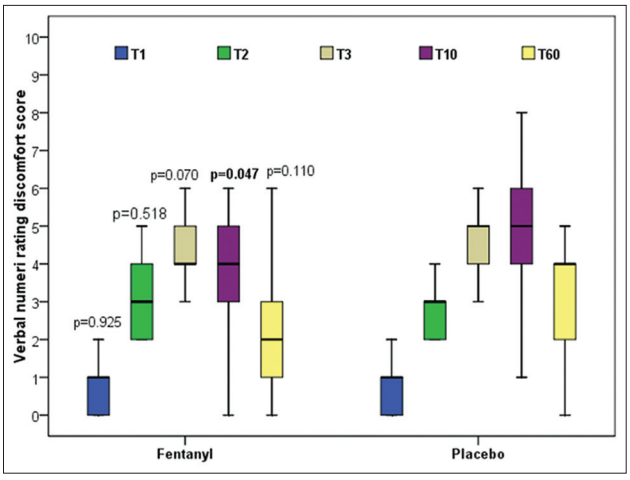

Figure 2: Comparison of discomfort: Fentanyl versus placebo. T1: At base line; T2: After initial local anesthetic injection; T3: Immediately after the procedure, the patient was asked to report the peak pain experienced during the procedure; T10: 10 minutes after completion of the procedure; T60: 60 minutes after completion of the procedure, *P*<0.05 consider significant in comparison to placebo group

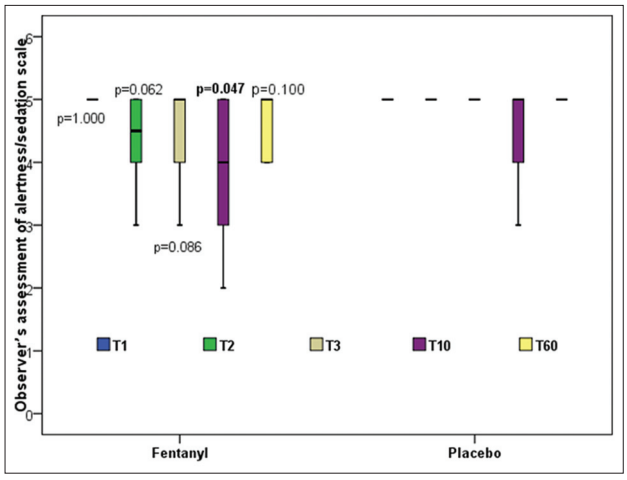

Figure 3: Comparison of sedation score: Fentanyl versus placebo. T1: At base line; T2: After initial local anesthetic injection; T3: Immediately after the procedure, the patient was asked to report the peak pain experienced during the procedure; T10: 10 minutes after completion of the procedure; T60: 60 minutes after completion of the procedure, *P*<0.05 consider significant in comparison to placebo group

either alone or in combination with sedation before or during a CVC depending on the pain intensity at the beginning of the procedure. However, they suggested use of preemptive analgesia to avoid central sensitization which can lead to persistent pain that continues for some time after a noxious event. Puntillo,[10] in her study on pain management in critically ill surgical patients has reported that pain relief was inferior with morphine if its administration was not timed to peak effect. In our study we provided base line analgesia with preprocedural infusion of fentanyl and found that fentanyl provides superior analgesia for all procedural steps (T2 through T10) when compared with placebo group.

Short acting opioid have been advocated for brief painful ICU procedures. Joshi *et al*.,[11] used bolus fentanyl and sufentanil 10 min before chest tube removal and demonstrated a low mean pain intensity score compared with the control group at 5 and 20 min in the postprocedural period.

Burlacu and *et al*.[7] used three different rates of remifentanil infusion for patients undergoing insertion or removal of long-term tunneled central venous access devices during sedation with propofol and field infiltration with LA and found all were equally analgesic-efficient. However, most of the patients in their study group required a bolus of rescue analgesic indicating that a simple infusion regimen may not be sufficient to meet the analgesic demand for different procedural step. In contrast to their study,[7] our procedure was of shorter duration and probably the magnitude of pain also would have been less compared to tunneled catheterization where not only LA infiltration, but also subcutaneous tunneling induces greater pain. Hence we choose to use short single bolus fentanyl infusion over a continuous infusion throughout the procedure and yet we achieved the targeted decrease in pain score that was prospectively agreed on at the time of study power calculation.

In our study, fentanyl was able to reduce procedure specific pain at T2, T3 and T10 time points in comparison to placebo group ($P < 0.005$). In contrast, we did not find any statistical difference in discomfort level as assessed by VNRDS between fentanyl and control group except in the immediate postprocedure period (10 min after CVC). This differential action of fentanyl can be partly explained by multidimensional model of procedural pain.[8] Fentanyl, which acts as a pure opioid analgesic mainly, affected the sensory-discriminative component of the pain and an inappreciable magnitude of effect in attenuating the motivational-affective and cognitive component of pain.

Fentanyl as an intraoperative analgesic agent has good track record owing to the cardiovascular stability it provides, even in critically ill patients.[12,13] However, the major obstacle in using fentanyl in the ICU for procedural sedation is its potential for respiratory depression. We have used a single bolus preprocedural fentanyl infusion and not encountered any clinically significant respiratory depression (requirement for intervention with naloxone administration, resuscitation with bag-mask ventilation) which are common after continuous background IV fentanyl infusion.[14,15]

In our study only three patients from fentanyl group had adverse respiratory events; two patients had SpO_2 < 92% and a simple head tilt-chin lift maneuver had to be applied to maintain saturation above 98% and one patient had SpO_2 < 92% and RR < 8 and required head tilt-chin lift maneuver along with a single time nasopharyngeal stimulation to maintain the RR and oxygen saturation.

The major limitation of the study is the nonuniformity in the indication for CVC in the study sample chosen. For example, patients who required a chemotherapeutic agent (caustic drugs) or parenteral nutrition were frequent visitors to the hospital for their illness and well acquainted with different painful hospital procedures in the past. These patients might have had an entirely different perception of pain and discomfort during their procedures than the eligible patients who came to the hospital for the 1st time. Nevertheless, the numbers of patients requiring CVC for different indications were equally distributed among groups.

Conclusion

For central venous access procedures using nontunneled CVC, preprocedural fentanyl bolus infusion (2 μg kg^{-1}) along with field infiltration of LA was associated with less procedural pain than placebo. Though fentanyl generally trended towards better discomfort score than placebo, these failed to reach statistical significance except at the end of procedure. Finally, considering the fact that, use of preprocedural fentanyl is associated with significantly higher incidences of adverse cardiovascular events and desaturation in an alarming number of patients, a sufficiently large multi-center study need to be conducted to interpret the positive effects of preprocedural fentanyl on pain and discomfort during CVC.

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How to cite this article: Samantaray A, Rao MH. Effects of fentanyl on procedural pain and discomfort associated with central venous catheter insertion: A prospective, randomized, double-blind, placebo controlled trial. Indian J Crit Care Med 2014;18:421-6.

Source of Support: Nil, **Conflict of Interest:** None declared.