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Enhancing oncology and radiotherapy practice: The advantages of propofol and fentanyl in curettage procedures

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ABSTRACT

Propofol and fentanyl have broadly used alone or in combination to induce sedation or anesthesia. The current study aims to assess the additive impact and economic benefit of using combination of propofol and fentanyl in elective curettage cases in Iraq. A total of 75 women were recruited to perform clinical trial between 1st January and 10th March 2023 at the department of gynecology and obstetrics in the Baghdad teaching hospital, Iraq. The sample was subdivided equally into three groups and received different doses of propofol alone (GI), Fentanyl alone (GII), and combination of propofol and fentanyl (GIII) respectively. The dose required for propofol to induce general anesthesia declined to 1.4 mg/kg -1.5 mg/kg instead of 2.5mg/kg, and 2 µg/kg instead of 8 µg/kg for fentanyl in the combination. Out of 25 cases, 19 (76%) patients being unconscious in a time of two minutes as a result of additive effect. Moreover, the cost evaluation showed a cost saving of USD 0.09/minute for every operated curettage weighing 65kg and average surgical time of 21.57+11.06 minutes. The combination of propofol and fentanyl is effective for sedation and anesthesia and cost saving.

Keywords: propofol, fentanyl, additive effect, anesthesia, cost saving, curettage

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INTRODUCTION

Propofol is a commonly used intravenous hypnotic agent in non-cardiac surgery due to its rapid onset of action and short duration of effect. It is a lipophilic compound that undergoes rapid metabolism and elimination, which allows for fast recovery times [1]. However, using propofol alone may require higher doses, which can increase the risk of adverse effects. Several unwanted hemodynamic effects have been reported, particularly in patients who are already have preexisting cardiovascular disease [2].

Older patients had higher sensitivity to the impact of propofol due to age-related changes in physiology. A lower induction dose of propofol (1 mg/kg) in patients over 55 years or those with a high anesthetic risk is recommended. Concomitant administration of opioids, such as fentanyl, during anesthesia induction, can allow for dose reduction and minimize adverse reactions. Opioids such as fentanyl are used to provide analgesia during sedation [3, 4]. Opioids and propofol have pharmacological synergy, meaning that when used together, they can produce greater sedation than either drug alone. By reducing the amount of propofol needed to achieve adequate sedation, the risk of propofol-associated hypotension can be reduced [5].

Overall, the combination of opioids and propofol can be a useful strategy for achieving safe and effective anesthesia induction with minimal hemodynamic instability. In another way, the combination of these drugs can produce moderate sedation and relieve pain and discomfort during procedures, while also allowing for a short recovery time. However, the use of sedation during surgery can facilitate the procedure and improve patient satisfaction, but it also comes with increased costs and risks of adverse events such as cognitive function impairment, delayed hospital discharge, and restrictions in daily activities. Therefore, as with any drug combination, careful dosing and monitoring are necessary to minimize the risk of adverse effects [6, 7]. Additionally, there is still debate in the literature about which drug or combination of drugs is best for achieving safe and effective sedation with minimal adverse effects. The choice of sedative drugs and doses should be individualized based on factors such as the patient's age, medical history, and the type of procedure being performed [8]. This study aimed to assess the additive and economic impact of using the propofol and fentanyl in induction general anesthesia among the curettage cases at the Baghdad teaching hospital, Baghdad, Iraq.

PATIENTS AND METHODS

Study design and setting

A prospective randomized comparative clinical trial was conducted between January and February 2023 at the department of obstetrics and gynecology, Baghdad teaching hospital, Baghdad, Iraq.

Sample size

The sample size calculator produced 84 respondents, "using a margin of error of ± 7%, a confidence level of 80%, and a 50% response distribution".

Randomization and patient selection

A sample of 75 pregnant women were eligible and scheduled for elective curettage under general anesthesia. The surgical staff, anesthesia drugs and the anesthesiologists were blinded. The eligible patients were randomly allocated into one time (2 minutes) three groups (each comprised of twenty-five patients), and these groups (GI, GII, GIII) were each divided into five dose subgroups (SG), resulting in fifteen one-time-dose groups (Table 1). The GI received Propofol, The GII received fentanyl and the GIII received combination of propofol and fentanyl.

Tab. 1. Study sample divided into fifteen one time-dose groups (n=75)

GI N (25)	Propofol Dose (mg/kg)	GII N (25)	Fentanyl Dose (mg/kg)	GIII N (25)	Combination of Propofol and Fentanyl Dose (mg/kg)
5	1	5	0.007	5	0.9 + 0.002
5	1.25	5	0.0075	5	1 + 0.002
5	1.5	5	0.008	5	1.3 + 0.002
5	2	5	0.0085	5	1.4 + 0.002
5	2.5	5	0.0095	5	1.5 + 0.002

Inclusion and exclusion criteria

All women scheduled for elective curettage, aged 18 years -49 years, scored (I-II) according to the American Society of Anesthesiologists (ASA) Physical Status Classification System have no bleeding tendency, and willing to participate were included in the study. Dilation and Curettage (D&C) are the surgical work devoted to dilate the cervix and removing the contents of the uterine cavity. Several reasons were listed for D&C including the diagnostic, therapeutic, miscarriage, abortion, treatment of molar pregnancy, retained pregnancy tissue, and prolonged or excessive vaginal bleeding. However, old age patients and those with preoperative severe bleeding, history of drug allergy, low blood pressure, cardiac or pulmonary disease and unwilling to participate were excluded from the study.

Anaesthesia protocol

All patients underwent the necessary clinical and laboratory examination after obtaining the oral and written consent form to ensure the patient's suitability for surgery and study. Premedication options have been excluded to prevent the possible risk of interference with the anesthetic drug. The standard measures have been implemented during the surgery such as monitoring the body vital signs, and close control of blood pressure, electrocardiographic, capnography and saturation of arterial oxygenation".

In the GI, the general anesthesia was induced (for each five patients) by intravenous injection of propofol at a dose of (1;1.25;1.5;2;2.5 mg/kg), over 20-40 s in an intravenous infusion. Induction time was defined as the duration between the beginning of bolus injection and disappearance of the eyelash reflex. Loss of consciousness was recorded when patients became unresponsive to verbal commands of opening their eyes within 2 minutes. If unconsciousness was not attained after 2 min, additional dose of propofol (20mg boluses) should be given. In the GII, the Fentanyl was injected at a dose of (0.007; 0.0075; 0.008; 0.0085; 0.0095mg/kg), over 20 s-40 s in an intravenous infusion. In the GIII, the combination of propofol and fentanyl was injected at a dose of (0.9+0.002); (1+0.002); (1.3+0.002); (1.4 0.002); (1.5+0.002) mg/kg, over 20s -40s in an intravenous infusion (Table 1).

Statistical analysis

Data was analyzed using SPSS version 16. The mean and Standard Deviation (SD) was recruited to present the quantitative variables, while the frequency and percentage were used to present the qualitative variables. An independent sample t-test and Chi-square tests were used in bivariate analysis. The statistically significant was considered below 0.05.

RESULTS

Eighty-four patients checked for study's eligibility. Nine patients were excluded due to inclusion criteria, and seventy-five patients were randomly distributed to receive either propofol, fentanyl or combination of them. The participants' characteristics presented in Table 2. The mean age of women was 31.20 + 6.17 years ranged from 18 years-45 years. The mean of women's' weight was 65.03 + 4.21. The average time for surgery was 21.57 + 11.06 minutes. Results showed no significant differences between groups for "mean of age, weight, and duration to perform surgery, and the ASA status" (P>0.05).

Tab 2. patients' characteristics in three studied groups (n=75)

Patients' characteristics	GI (n-25)	GII (n=25)	GII(n=25)	*P*-value
Age (years)	30.71 ± 6.82	31.10 ± 7.36	30.12 ± 6.05	0.205
Weight (kg)	65.32 ± 5.72	64.55 ± 4.08	65.25 ± 5.01	0.312
ASA status				0.076
I	23 (92.0)	24(96.0)	24 (96.0)	
II	2 (8.0)	1 (4.0)	1(4.0)	
Duration of surgery (minutes)	21.70 ± 11.02	22.01 ± 12.65	21.80 ± 11.73	0.231

ASA: American Society of Anesthesiologists

In GI, the average dose of propofol was 1.6 mg/kg. The number of unconscious patients in the studied five subgroups has increased ascending with the increased propofol dose in about two minutes. In a dose of 1mg/kg only one unconscious patients, however, all the five patients became unconscious with dose of 2.5 mg/kg. About 15 patients from the total 25 patients in sub-groups got loss of consciousness giving the percentage of 60% (Table 3).

Tab. 3. Dose-response difference between Propofol alone and combination of Propofol and Fentanyl

Propofol			Combination of Propofol and Fentanyl		
Dose (mg/kg)	No. of patients	unconscious patients n (%)	Dose (mg/kg)	No. of patients	unconscious patients n (%)
1	5	1 (20%)	0.9 + 0.002	5	2 (40%)
1.25	5	2 (40%)	1 + 0.002	5	3 (60%)
1.5	5	3 (60%)	1.3 + 0.002	5	4 (80%)
2	5	4 (80%)	1.4 + 0.002	5	5 (100%)
2.5	5	5 (100%)	1.5 + 0.002	5	5 (100%)
Total	25	15 (60%)	Total	25	19 (76%)

In GII, the average dose of fentanyl was 8 μg/kg. The gradual increase in the fentanyl dose through the five studied sub -groups resulted in an unsteady increase in the number of unconscious patients in two minutes. About 12 patients from the 25 patients in the sub-groups became unconscious and the percentage declined below fifty (48%) (Table 4).

Tab. 4. Dose-response difference between Fentanyl alone and combination of Propofol and Fentanyl

Fentanyl			Combination of Propofol and Fentanyl		
Dose(mg/kg)	No. of patients	un	Dose (mg/kg)	No. of patients	Loss of consciousness
0.007	5	1 (20%)	0.9 + 0.002	5	2 (40%)
0.0075	5	1 (20%)	1 + 0.002	5	3 (60%)
0.008	5	3 (60%)	1.3 + 0.002	5	4 (80%)
0.0085	5	3 (60%)	1.4 + 0.002	5	5 (100%)
0.0095	5	4 (80%)	1.5 + 0.002	5	5 (100%)
Total	25	12 (48%)	Total	25	19 (76%)

Unlike to GI and GII, the GIII showed significant increase in the number of unconscious patients when a relatively low doses of combination of propofol and fentanyl used. The dose of propofol declined to 75.0% of the average dose (1.6mg/kg) to be 1.2mg/kg and the dose of fentanyl was declined to 25% of the average dose (8 μg/kg) to be 2 μg/kg in the combination regime. The additive effect resulted in almost 19 (76%) of 25 tested cases in the sub-groups to be unconscious in a time of two minutes (Table 2, 3). Further, the number of unconscious patients was higher among those taking Fentanyl and Propofol than those taking propofol alone ($P<0.05$). There was significant loss of consciousness among patients taking Fentanyl and Propofol than those taking Fentanyl alone ($P<0.05$).

Costing technique

In term of costing technique, medicines (drugs) are classified among the direct cost's items because they are most likely directly attributed to the patient's care [9]. The estimated cost was calculated based on the average weight (65 kg) of women included

in this study (Table 5, 6). Considering the various prices of medications worldwide including Iraq, the researchers adopted the average prices offered by some companies in the United States. The price of propofol (10mg/ml) is (USD 0.32), and (USD 0.032 per 1mg). The price of fentanyl (50mcg/ml) is (USD1.66), and (USD 33.2) per 1mg.

Table 1 provides an overview of the demographic characteristics of the study participants across different thyroid disease categories and a control group. The cohorts were comparable in size, each consisting of 30 participants. While age was similarly distributed across all groups, indicated by a non-significant P-value of 0.52, the gender distribution was marginally different, but also not statistically significant with a P-value of 0.0549.

Tab. 5. Cost of propofol and fentanyl for patient weighing 65kg

No.	Propofol Dose (mg/kg)	Cost per patient (USD)	Fentanyl Dose (mg/kg)	Cost per patient (USD)	Total cost (USD)
SG1	1mg X 65kg X 0.032 $	2.08	0.007mg X 65kg X 33.2 $	4.327	6.407
SG2	1.25mg X 65kg X 0.032 $	2.6	0.0075mg X 65kg X 33.2 $	4.328	6.928
SG3	1.5mg X 65kg X 0.032 $	3.12	0.008mg X 65kg X 33.2 $	4.328	7.448
SG4	2mg X 65kg X 0.032 $	4.16	0.0085mg X 65kg X 33.2 $	4.329	8.489
SG5	2.5mg X 65kg X 0.032 $	5.08	0.0095mg X 65kg X 33.2 $	4.329	9.409

Tab. 6. Cost of combination of propofol and fentanyl for patient weighing 65kg

No.	In combination Propofo Dose (mg/kg)	Cost per patient (USD)	In combination Fentanyl Dose (mg/kg)	Cost per patient (USD)	Total cost (USD)
SG1	0.9mg X 65kg X 0.032 $	1.87	0.002mg X 65kg X 33.2 $	4.32	6.19
SG2	1.0mg X 65kg X 0.032 $	2.08	0.002mg X 65kg X 33.2 $	4.32	6.40
SG3	1.3mg X 65kg X 0.032 $	2.70	0.002mg X 65kg X 33.2 $	4.32	7.02
SG4	1.4mg X 65kg X 0.032 $	2.91	0.002mg X 65kg X 33.2 $	4.32	7.23
SG5	1.5mg X 65kg X 0.032 $	3.12	0.002mg X 65kg X 33.2 $	4.32	7.44

In the subgroup 5 (SG5) all patients who received propofol alone got loss of consciousness within two minutes at a dose of 2.5mg/kg. The calculated cost for one patient is USD 5.08. In contrast, all patients in the SG5 need a lowering dose of propofol (1.5mg/kg) when combined with declined dose (0.002mg/kg) of fentanyl to reach the state of loss of consciousness within two minutes. The calculated cost for one patient is USD 3.12. (Figure 1).

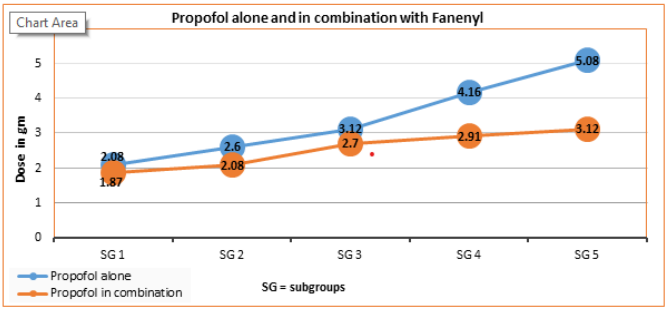

Fig. 1. Trend of using propofol alone and in combination with Fentanyl

The estimated cost saving for using propofol in one patient = Propofol alone – propofol in combination Cost saving (USD 5.08- USD 3.12) is USD1.96 per woman weighing 65kg (average). Considering the average curettage surgical time is 21.57 + 11.06 minutes, the cost saving of using 1.4-1.5mg/kg of propofol in combination with 2mcg/kg is (USD1.96/21.57 min = USD 0.09 per minute for each woman weighing 65kg underwent elective curettage under GA.

DISCUSSION

Propofol and opioids like fentanyl are often used together for anesthesia and sedation purposes. The combination of these drugs has been shown to have an additive effect, meaning that the effects of the drugs together are greater than the effects of either drug alone [10-12]. On the other hand, propofol-fentanyl combination has been reported to produce a more stable hemodynamic profile, with a decrease in heart rate, blood pressure, and cardiac output, which can be advantageous in patients with hypertension or cardiac disease [11, 12]. In this study pharmacodynamics of the propofol and fentanyl drugs altered by combination. The combination had a synergistic effect, meaning that the combined effect was greater than the effect of each drug when given alone. Results of this study showed a decreased in dose requirement for both drugs in the combination. Specifically, the dose of propofol decreased by 75% and the dose of fentanyl decreased by 25% when the two drugs were used in combination. Furthermore, the study found that the response rate to the combination of propofol and fentanyl was 76%, which is higher than the response rate to either drug alone (60% for propofol and 48% for fentanyl). The combination of the two drugs improved the overall sedative and analgesic effect. Similar findings to current study were reported by Ben Shalom et al. and Ground et al. [13, 14]. The study by De Fátima and colleagues comparing intubating conditions

using different drug combinations is also informative [15]. The finding that there was no significant difference in intubating conditions between using thiopentone and fentanyl versus propofol and fentanyl, suggests that the combination of fentanyl and propofol may be an effective alternative for certain procedures or situations. Singh Bajwa et al. reported that the propofol-ketamine and propofol-fentanyl combinations provide rapid and safe induction of anesthesia, and good analgesia with minimal side effect such as respiratory depression [16]. However, they may have different effects on hemodynamic parameters, depending on the patient population and dosage used. Chang and Yang compared propofol plus fentanyl sedation to propofol alone sedation during painless gastrointestinal endoscopy, and have reported similar findings to the current study [17]. The authors found that propofol plus fentanyl sedation results in fewer doses of propofol and shorter recovery time than propofol alone sedation. Additionally, propofol plus fentanyl sedation has been reported to provide better pain control and patient satisfaction during the procedure. The consistency in findings across multiple studies can help to strengthen the evidence supporting the use of the combination of propofol and fentanyl for sedation and anaesthesia. Economic evaluations are an important aspect of healthcare decision-making, as they can help to inform decisions about the most cost-effective approaches to care. The findings of this study provide additional evidence to support the use of the propofol/fentanyl combination. The cost saving of using 1.4 mg/kg -1.5mg/kg of propofol in combination with 2mcg/kg is (USD1.96/21.57 min = USD 0.09 per minute for each woman weighing 65kg who underwent elective curettage under GA. Similarly, Sherry et al. conducted an economic evaluation study to compare the combination of propofol and fentanyl with the combination of fentanyl and midazolam in post-operative cardiac surgery patients in the intensive care unit [18]. ₵e finding that the total cost was 13.3% less for the propofol/fentanyl group compared to the fentanyl/midazolam group suggests that the propofol/fentanyl combination may be a cost-effective option for sedation in these patients. Van Noord et al. found that the cost of using propofol (USD 0.12/min) for anesthetic maintenance was lower than sevoflurane (USD 0.18/min), and desflurane (USD 0.48/min) [19]. Overall, the combination of propofol and fentanyl appears to have potential benefits in terms of both clinical effectiveness and economic value. However, the results of this study may not be generalizable to all patients or situations, and caution should always be taken when administering any medication or combination of medications.

CONCLUSION

The combination of propofol and fentanyl has been shown to be effective for sedation and anesthesia in various clinical settings. Both required large doses (2.5 mg/kg of propofol and 8μg/kg of fentanyl) to produce unconsciousness in two minutes among an elective curettage patient. In contrast, the combination of Propofol and Fentanyl has an additive effect and can produce better outcomes with smaller doses (1.4 mg/kg -1.5 mg/kg of propofol and 2μg/kg of fentanyl) compared to either drug alone. Additionally, economic evaluations have suggested that the combination may be cost-effective in certain patient populations. However, as with any medication, the use of combination should be carefully considered and monitored by healthcare professionals to ensure patient safety and optimal outcomes.

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