ORIGINAL ARTICLE

# Comparison of intraoperative hemodynamic and recovery pattern between opioid free and opioid based anaesthesia for minor day care gynaecological procedures

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**Abstract**

*Background:* Dexmedetomidine has been compared to fentanyl for sedation many times but not as sole analgesic agent as a part of Opioid Free Anesthesia (OFA). Dexmedetomidine, when used in balanced OFA for major surgeries can result in delayed recovery with hemodynamic instability. In this study we compared dexmedetomidine with fentanyl in Total Intravenous Anesthesia (TIVA) with propofol for minor gynecological procedures. *Aim and Objectives:* To compare propofol and dexmedetomidine combination versus propofol and fentanyl combination for minor day care gynecological procedures. *Material and Methods:* Fifty-six patients were randomly divided into two groups. Group D received intravenous dexmedetomidine in the dose of 1 μg/kg and Group F received intravenous fentanyl in the dose of 2 μg/kg. All the patients were induced with propofol 2 mg/kg and maintained with 0.5 μg/kg of propofol top up as required. Recovery and discharge time, number of propofol top ups required, intraoperative hemodynamics and respiratory parameters were compared between the groups. *Results:* Statistical analysis was done using Chi square and independent t tests. Group D had significantly reduced recovery time (p=0.019) and time to discharge (p=0.001). Group D required more propofol top ups (p=0.001). Apart from initial 15 minutes from start of infusion of dexmedetomidine, incidence of hypotension was comparable between the groups. There was no incidence of bradycardia in any group. *Conclusion:* Opioid free TIVA with dexmedetomidine and propofol provides faster recovery and discharge with stable hemodynamics for minor gynecological surgeries

**Keywords:** Dexmedetomidine, Fentanyl, Opioid Free Anesthesia

## Introduction

Day care surgeries are preferred by the patients, healthcare providers and health policy makers due to its various benefits to each group [1]. The emphasis has been given to perform most of the adult and even pediatric surgeries on day care basis [2]. Day care surgeries demand anesthetic agents and techniques which provide adequate analgesia, early recovery, and discharge from the hospital with minimum stress and maximum comfort to the patients [2]. The most commonly used combination for day care anesthesia is propofol with fentanyl. Due to its property of rapid recovery, propofol is being used as a primary anesthetic agent for the Total Intravenous Anesthesia (TIVA) combined with opioids.

Today, Opioid Free Anesthesia (OFA) is being considered whenever possible as it reduces the possibility of opioid addiction and development of chronic surgical pain as well as postoperative hyperalgesia, nausea/vomiting, delayed recovery, and discharge [3].

Dexmedetomidine, an alpha 2 adrenergic agonist has been proven to reduce opioid requirements intra-operatively and is being used in opioid free balanced anesthesia. Dexmedetomidine reduces postoperative pain intensity, opioid consumption, nausea and vomiting without any delay in recovery, thus making it an ideal agent for day care surgery [4].

Despite its anxiolytic, sympatholytic, analgesic and sedative properties, dexmedetomidine has failed as a sole anesthetic agent for minor surgeries [5]. OFA with dexmedetomidine for major surgeries have shown delayed recovery times and hemodynamic instability [6-7]. Those surgeries were of prolonged duration which needed larger doses and continuous infusions of dexmedetomidine. Hence, more evidence is needed to define risk benefit strategies for OFA with dexmedetomidine [7]. No previous study has compared propofol-fentanyl TIVA with propofol-dexmedetomidine OFA combination for recovery and discharge profile in minor procedures.

The aim of the study was to compare propofol and dexmedetomidine combination versus propofol and fentanyl combination for minor day care gynecological procedures. It was hypothesized that dexmedetomidine would be better than fentanyl as an adjuvant to propofol in TIVA.

**Material and Methods**

This was a prospective randomized double blinded study conducted over a period of one year, after receiving approval from the Institutional Ethics Committee. The trial was registered with clinical trial registry of India (CTRI/2019/03/017897). Patients undergoing elective minor gynecological procedure between 18 to 60 years of age belonging to American Society of Anesthesiologist (ASA) status I and II were included in the study. Patients with extremes of Body Mass Index (BMI <18 or >30), on chronic opioid treatment or chronic pain conditions, with cardiovascular disease, hypertension and not willing to participate in the study were excluded from the study. Informed and written consent regarding participation in study was obtained preoperatively after explaining to the patients in their preferred language. All patients were fasted for a period of 8 hours prior to surgery. Patients were randomly divided into two groups, Group D and Group F by a computer- generated list of random numbers. Patients were shifted inside Operation Room (OR) and intravenous access was established using 18G cannula. Electrocardiogram (ECG), Non-Invasive Blood Pressure (NIBP) and pulse Oximeter ($SpO_2$), End tidal Carbon dioxide ($EtCO_2$) monitors were connected and baseline parameters were noted. Group D patients received injection dexmedetomidine (Dextomid 100 mcg/ml, Neon laboratories Ltd, India) in dose of 1 µg/kg in 100 ml normal saline as infusion over ten minutes. Group F patients received injection fentanyl (Verfen, Verve Healthcare Ltd, India) in dose of 2 µg /kg in 100 ml normal saline as infusion over ten minutes. Patients in both groups were induced with injection propofol (Profol, Baxter Pharmaceuticals India) 2 mg/kg. Drugs were given by an independent investigator who was not involved in monitoring of patient. Supplemental 5 liters per minute of oxygen was given via face mask in all cases. Heart Rate (HR), Respiratory Rate (RR), ECG, $SpO_2$, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP) and $EtCO_2$ monitoring was done every 5 minutes intraoperatively. Additional top ups of propofol in doses of 0.5 mg/kg were given in

both the groups if there was increase in HR by 10% from baseline, more than 10% rise in blood pressure from baseline, respiratory rate more than 5 breaths/minute from baseline. Total number of propofol top ups required were noted. Time of last propofol dose given was noted. Time of eye opening was noted. Time between last dose of propofol and eye opening was taken as recovery time. Incidence of bradycardia (HR < 60/min) and hypotension (more than 20% fall in MAP) were noted. Hypotension was treated with intravenous fluids and vasopressors. Prophylactically diclofenac rectal suppository 100 mg was given for postoperative analgesia. Hemodynamic stability of patients was assessed and were shifted to recovery for further monitoring. Monitoring was done in the recovery room every 15 minutes for the next few hours by using Post Anesthesia Discharge Scoring System (PADSS) [8]. PADSS considers six variables: vital signs, ambulation, nausea/vomiting, pain, bleeding and voiding. Each variable is given a score ranging from 0 to 2. Score of $\geqslant 9$ with score for vital signs as 2 were set as discharge criteria. Time taken from the eye opening to meet discharge criteria was taken as discharge time and it was noted.

Primary outcome of the study was to compare time to meet discharge criteria between two groups. Secondary outcomes were to compare the recovery time, to compare the number of propofol top ups needed and to compare hemodynamic stability in the intra-operative period.

Sample size calculations were done based on previous study in which mean recovery time of 8.7 and SD of 1.39 minutes in Group 1 and mean of 10.56, SD of 1.63 in Group 2 was noted. Twenty-four patients were needed for significance of 5% and 80% power of study [9]. Twenty-eight patients were included per group to avoid possible dropouts. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 23.0. (SPSS Version 23.0, IBM, Armonk, NY, USA). Kolmogorov Smirnoff test was used to assess the normality of data. Chi square test and Student's t-test were used for comparing the results. Value of p less than 0.05 was considered as statistically significant for a two-sided test.

**Results**

In this prospective randomized controlled double blinded study, we included and analyzed 56 patients. Among the 72 who were screened for eligibility, 56 patients were enrolled into two groups with 28 patients in each group. All 28 patients in each group received allocated study medication and were analyzed. There was no patient lost to follow up or any discontinuity in study protocol in both the groups.

The demographic parameters were comparable between the groups (Table 1). Group D showed significantly better PADSS scores at all the times of measurement (Table 2). All patients in Group D attained discharge criteria of PADSS more than or equal 9 within 60 minutes while only 50% of the patients in Group F attained it in one hour. The recovery time (time from last dose of propofol to eye opening) was significantly faster in Group D even though number of propofol top ups were more in Group D (Table 1). Recovery time was 25 minutes in Group D compared to 32 minutes in Group F. This difference was statistically significant with p value of 0.019 (CI=13.06-1.22). The time to reach discharge criteria was 39.64 minutes in Group D which was significantly lesser compared to 71.79 minutes in Group F (CI =37.6-26.6). Incidence of intraoperative hypotension was

more in Group D at 10 and 15 minutes interval. At 10 minutes, it was significantly more in Group D than Group F (p=0.04). However, the incidence of hypotension in remaining intraoperative period was comparable between the groups (Table 3). At 10 and 15 minute interval, Group D had fall in SBP (Fig. 1). The fall in SBP and DBP after 15 minutes was comparable between the groups. HR trend is shown in Fig. 2. There was no incidence of bradycardia in any group. RR and $SpO_2$ and $EtCO_2$ were comparable between the groups at all time intervals.

**Table 1: Comparison of patient characteristics**

| Variables | | Group D (Mean ± SD) | Group F (Mean ± SD) | p |
|---|---|---|---|---|
| **Age (years)** | | 40.00 ± 11.26 | 39.71 ± 9.78 | 0.92 |
| **Weight (kg)** | | 60.93 ± 12.59 | 61.64 ± 8.27 | 0.80 |
| **Height (cm)** | | 157.32 ± 6.56 | 157.50 ± 7.73 | 0.93 |
| **BMI ($kg/m^2$)** | | 24.50 ± 4.32 | 24.89 ± 3.07 | 0.69 |
| **Duration of surgery (minutes)** | | 27.86 ± 11.17 | 29.29 ± 11.44 | 0.64 |
| **Recovery time (minutes)** | | 25.54 ± 11.25 | 32.68 ± 10.84 | 0.019 |
| **Time to reach discharge criteria (to reach PADSS ⩾9) (minutes)** | | 39.64 ± 9.32 | 71.79 ± 11.07 | 0.001 |
| **No of propofol top ups** | **1** | 5 (17.85%) | 3(10.71%) | 0.001 |
| | **2** | 1 (3.57%) | 0 | |

**Number of patients (% of patients) requiring top ups*

**Table 2: PADSS distribution among the groups at different time periods**

| Time in minutes | Group D Mean ± SD | Group F Mean ± SD | p | CI |
|---|---|---|---|---|
| **15 minutes** | 7.50 ± 0.79 | 6.46 ± 0.92 | 0.001 | 0.575-1.497 |
| **30 minutes** | 8.18 ± 0.61 | 6.61 ± 0.74 | 0.001 | 1.208-1.934 |
| **45 minutes** | 9.00 ± 0.000 | 7.29 ± 0.60 | 0.001 | 1.487-1.942 |
| **60 minutes** | 9.54 ± 0.51 | 8.36 ± 0.95 | 0.001 | 0.770-1.587 |

*SD - Standard deviation, CI- confidence interval*

**Table 3: Incidence of intraoperative hypotension**

| Time in minutes | Group D Number (%) | Group F Number (%) | p |
|---|---|---|---|
| **5 minutes** | 0 | 0 | -- |
| **10 minutes** | 3 (10.71) | 0 | 0.04 |
| **15 minutes** | 6 (21.42) | 1(3.57) | 0.08 |
| **20 minutes** | 5 (17.85) | 1(3.57) | 0.19 |
| **25 minutes** | 4 (14.28) | 2 (7.14) | 0.68 |
| **30 minutes** | 3 (10.71) | 2 (7.14) | 0.54 |
| **35 minutes** | 1(3.57) | 1(3.57) | 0.51 |
| **40 minutes** | 2 (7.14) | 0 | 0.12 |
| **45 minutes** | 2 (7.14) | 0 | 0.17 |
| **50 minutes** | 1(3.57) | 0 | 0.49 |

*% - Percentage of patients*

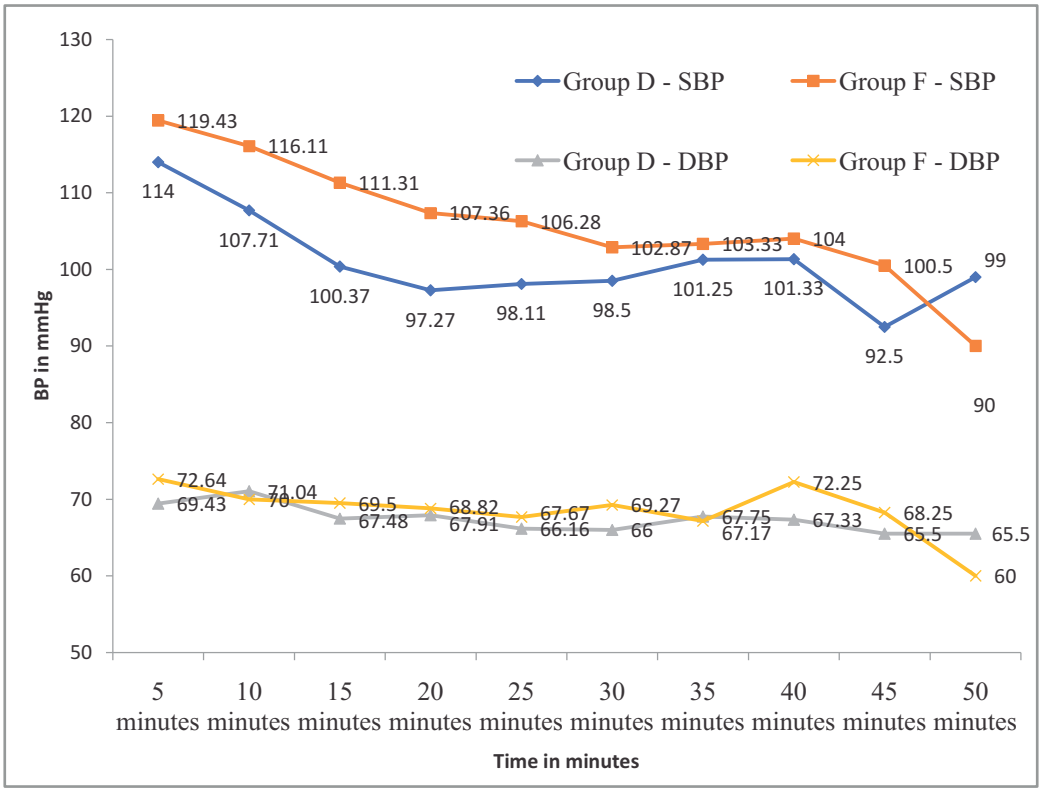


**Figure 1: Distribution of systolic and diastolic blood pressure between the groups**

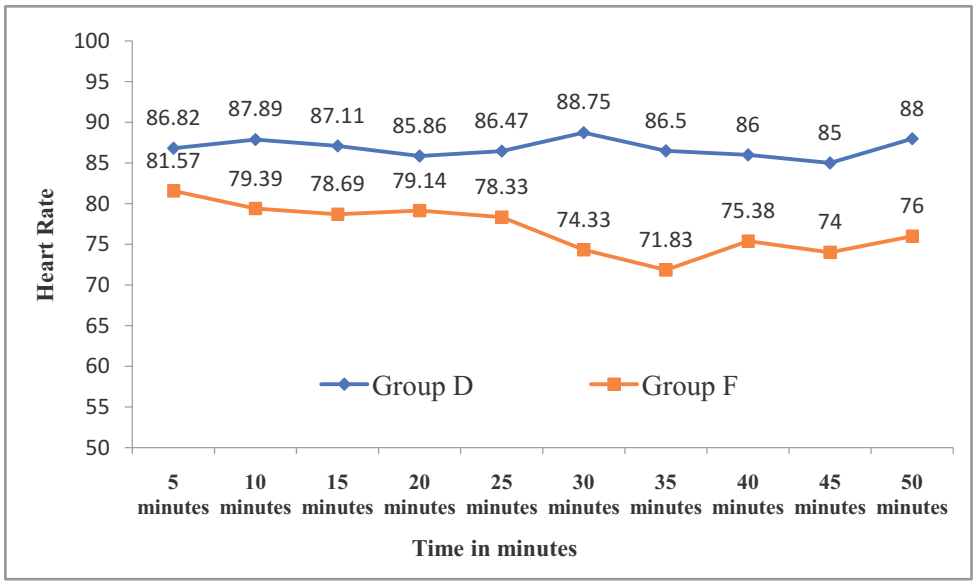


**Figure 2: Comparison of heart rate between the groups**

## Discussion

In this study we compared dexmedetomidine and fentanyl as an adjuvant to propofol in TIVA for day care gynecological surgeries. We found that recovery and discharge times were significantly less in dexmedetomidine group. Apart from initial 15 minutes, when hypotension was more with dexmedetomidine group, both groups were hemodynamically stable.

Dexmedetomidine is a potent alpha-2 adrenergic receptor agonist and produces its analgesic effect by inhibition of norepinephrine release from presynaptic neurons in the locus ceruleus, centrally mediated pain modification via the dorsal horn and inhibition of substance P [10]. However, the exact mechanism for its analgesic effects is still unclear and postulated as due to opioid sparing and altered pain perception [11]. Tomer *et al.* compared dexmedetomidine 1 µg/kg bolus followed by 0.6 µg/kg/h infusion as a sole sedative and analgesic agent with propofol, fentanyl and midazolam combination for surgeries of 45 minutes duration [5]. The requirement of intraoperative top up analgesic was more in dexmedetomidine group but the recovery was faster than fentanyl group which is similar to our findings. Incidence of bradycardia was more with dexmedetomidine group whereas in our study bradycardia was not seen in any group. Nolan *et al.* compared dexmedetomidine at 1 µg/kg over 10 minutes followed by 0.5 µg/kg/h as maintenance with 0.8 g/kg of fentanyl followed by propofol infusion at rate of 125 µg/kg/min [12]. They found that ambulation and discharge times were comparable between the groups. In our study, we found dexmedetomidine group had earlier discharge. We used dexmedetomidine only as loading dose and maintenance infusion was not given. Previous study with dexmedetomidine as loading dose followed by infusion found that recovery was faster with dexmedetomidine when compared with propofol-fentanyl. The average

duration of surgery was 45 minutes in that study [5]. In our study average duration of surgery was 30 minutes. Another study found that recovery, discharge times and hemodynamic parameters were comparable with control group when dexmedetomidine was given as 0.5 μg/kg bolus followed by 0.5 μg/kg/h for an average duration of 35 minutes [13].

Das *et al.* found that dexmedetomidine in 0.6 μg/kg/h with 2 μg/kg of fentanyl results in faster discharge times for day care surgeries when compared with control group [14]. The shorter discharge times were due to less postoperative complications like pain and nausea/vomiting. Incidence of reduction in MAP was seen intraoperatively with dexmedetomidine but not in postoperative period. In our study we monitored patients postoperatively with PADSS which included monitoring of vital signs, ambulation, nausea/vomiting, pain, bleeding and voiding every 15 minutes. The time taken to satisfy discharge criteria [score $\geqslant$ 9 with vitals score =2 (fall in BP <20% from preoperative)]was significantly less in Group D. Intraoperative MAP was lower in Group D at 10 minutes from start of infusion. Other than that, MAP was comparable between Group F and Group D at all times. Incidence of maximum fall of MAP at 10 and 15 minutes after infusion of 1 μg/kg of dexmedetomidine has been reported previously [15-16]. The previous study compared 1 μg/kg of loading followed by 0.5 μg/kg/h of maintenance of dexmedetomidine against 0.5 μg/kg of fentanyl for sedation for procedures of 10 minutes. Propofol 20 mg as bolus was used as top up and found that incidence of hypotension was comparable between groups but bradycardia was more in dexmedetomidine group [17]. Propofol top ups were more in fentanyl group. In our study, we did not notice bradycardia which may be due to lower doses of dexmedetomidine. Fentanyl group, in our study, required less propofol top ups as we used 2 μg/kg dose. Mausomi *et al*. compared 1 μg/kg of dexmedetomidine followed by 0.2 μg/kg/h maintenance against 1 μg/kg of fentanyl and concluded that time to reach desired sedation for shoulder manipulation procedure was faster with dexmedetomidine with higher level of analgesia [18]. In our study, we used 2 μg/kg of fentanyl and it required less propofol top ups than dexmedetomidine group. The top up requirement was in the initial phases of surgery which could be due to delay in time to reach adequate analgesic and sedative stage. The average time from last dose of propofol to eye opening was 25-30 minutes in both groups. Once the desired sedation level was achieved no group required additional top up but eye opening was delayed in fentanyl group as compared to dexmedetomidine group.

In our study, dexmedetomidine infusion for maintenance was not used and required sedation level was maintained by propofol top ups to achieve faster recovery and discharge times. Previous study in laparoscopic surgeries found that, 24 hour quality of recovery was better with dexmedetomidine compared with fentanyl. Both drugs were used as loading followed by maintenance infusion in that study [19]. Previous studies on OFA with dexmedetomidine have reported delayed recovery and hemodynamic instability when compared to fentanyl [6-7]. Those studies used 1-2 μg/kg of loading and maintenance dose. The recommended regime for dexmedetomidine is loading dose of 0.5-1 μg/kg followed by maintenance infusion of 0.2-1 μg/kg to achieve

desired sedation [11]. The distribution time is approximately 6 minutes with half- life of 2 hours and hence the dose must be titrated accordingly along with proper selection of surgeries.

Opioid free balanced anesthesia for major surgeries of long duration needs the risk benefit strategies [7]. Our results suggest that for surgeries of short duration, dexmedetomidine can be safely and effectively used as an alternative to opioids for day care surgeries. Our study has few limitations. Firstly, we did not monitor patient and surgeon satisfaction. Secondly, pain, nausea/ vomiting and sedation were not compared as separate parameters though they were monitored as a part of PADSS. Future studies are needed with different dosages of dexmedetomidine for various surgeries.

## Conclusion

Opioid free TIVA with dexmedetomidine and propofol provides faster recovery and discharge with stable hemodynamics compared to TIVA with fentanyl and propofol for minor gynecological surgeries.

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