Original Article

Propofol versus Ketofol for Sedation of Pediatric Patients Undergoing Transcatheter Pulmonary Valve Implantation: A Double-blind Randomized Study

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Abstract

Objective: The study was done to compare propofol and ketofol for sedation of pediatric patients scheduled for elective pulmonary valve implantation in a catheterization laboratory. **Design:** This was a double-blind randomized study. **Setting:** This study was conducted in Prince Sultan Cardiac Centre, Saudi Arabia. **Patients and Methods:** The study included 60 pediatric patients with pulmonary regurge undergoing pulmonary valve implantation. **Intervention:** The study included sixty patients, classified into two groups (n = 30). Group A: Propofol was administered as a bolus dose (1–2 mg/kg) and then a continuous infusion of 50–100 μg/kg/min titrated as needed. Group B: Ketofol was administered 1–2 mg/kg and then infusion of 20–60 μg/kg/min. The medication was prepared by the nursing staff and given to anesthetist blindly. **Measurements:** The monitors included heart rate, mean arterial blood pressure, respiratory rate, temperature, SPO_2 and $PaCO_2$, Michigan Sedation Score, fentanyl dose, antiemetic medications, and Aldrete score. **Main Results:** The comparison of heart rate, mean arterial pressure, respiratory rate, temperature, SPO_2 and $PaCO_2$, Michigan Sedation Score, and Aldrete score were insignificant ($P > 0.05$). The total fentanyl increased in Group A more than Group B ($P = 0.045$). The required antiemetic drugs increased in Group A patients more than Group B ($P = 0.020$). The durations of full recovery and in the postanesthesia care unit were longer in Group A than Group B ($P = 0.013$, $P < 0.001$, respectively). **Conclusion:** The use of propofol and ketofol is safe and effective for sedation of pediatric patients undergoing pulmonary valve implantation in a catheterization laboratory. However, ketofol has many advantages more than the propofol. Ketofol has a rapid onset of sedation, a rapid recovery time, decreased incidence of nausea and vomiting and leads to rapid discharge of patients from the postanesthesia care unit.

Keywords: *Catheterization laboratory, ketofol, pediatric patients, propofol, pulmonary valve implantation*

Introduction

The American Academy of Pediatrics Committee on drugs has issued guidelines categorizing pharmacological intervention into three levels: conscious sedation, deep sedation, and general anesthesia.[1] Conscious sedation refers to a state of depressed consciousness that "allows protective reflexes to be maintained" and permits appropriate response by the patient to physical stimuli or verbal command.[2] Conscious sedation was proved to be effective during cardiac catheterization procedures as an alternative to general anesthesia. Nonetheless, no specific regimen had gained a universal approval as the gold standard anesthesia. Few previously published reports described different regimens during cardiac catheterization of children, including single or combined medications.[3-11] These previously published reports included children with different diagnostic and interventional catheterization procedures within the same series. It is recognized that different interventional catheterization procedures carry different risks and hence anesthesia and sedation during the procedure is of ultimate importance. Transcatheter pulmonary valve implantation (TPVI) was categorized as one of the highest risk category procedures "risk category 4 on a scale of 1–4."[12]

There are no previous reports to assess the efficacy and safety of conscious sedation in such risky procedure. In our work, we will compare the efficacy and safety of two conscious sedation regimens (propofol

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alone vs. propofol and ketamine mixture) in patients undergoing TPVI.

Patients and Methods

During the initial phase of TPVI, the first ten patients were done under general anesthesia. We decided to shift to conscious sedation and assess its efficacy and safety. The work was approved by the local ethics and research committee in the Prince Sultan Cardiac Centre, and the procedures were done between 2009 and 2014. The inclusion criteria were patients with postoperative repair of tetralogy of Fallot who had pulmonary regurge and will be subjected to TPVI. Exclusion criteria included facial and neck physical abnormalities that could make airway support difficult, respiratory diseases, severe myocardial depression, fever, evidence of severe hepatic, renal, or endocrine dysfunction, epilepsy, morbid obesity, and history of allergy to the study medication.

A written informed consent was taken from those who fulfilled the criteria and agreed to be included in the study. The medication was prepared by the nursing staff and given to anesthetist blindly. Patients were randomly assigned into two groups (Group A: Propofol group and Group B: Propofol and ketamine mixture "Ketofol" group). Sixty patients were randomly divided into the two groups with thirty patients recruited in each group.

Patients of both groups were premedicated with midazolam orally (0.5 mg/kg) in the ward. In the preoperative area, two venous accesses were inserted under local anesthesia with 20- or 18-gauge cannula on the dorsum of the hand or forearm, one for the maintenance of intravenous fluids and the other for infusion of the study medications. Continuous heart rate, respiratory rate (chest wall movement), noninvasive blood pressure, invasive blood pressure from the femoral artery, pulse oximetry, and body temperature were monitored electronically every 5 min and arterial blood gasses every 30 min. Local anesthetic infiltration of the femoral puncture site with lidocaine 1% was done, and the femoral central venous line was inserted by the cardiologist.

Anesthesia

In Group A, the propofol was given intravenously, first as a bolus dose (1–2 mg/kg) and then a continuous infusion of 50–100 μg/kg/min titrated as needed. In Group B, ketofol was prepared as 1:1 mixture of ketamine and propofol in 20 ml syringe [10 ml ketamine (10 mg/ml) and 10 ml propofol (10 mg/ml), the concentration of ketamine or propofol after mixing is 5 mg/ml], and the syringe was shaked before fixation in the syringe pump. The ketofol was administered 0.2 ml/kg (1 mg/kg) as a bolus dose and continued an infusion of 25–50 μg/kg/min.

In both groups, fentanyl was given 1 μg/kg as a bolus dose as needed. All patients were kept during the procedures on oxygen mask.

Assessment

The sedation level of patients was assessed using the University of Michigan Sedation Scale (UMSS)[13] at the following time points, T0: Baseline (before sedation), T1: After administration of the drug, T2: On completion of the procedure, T3: During early recovery, and T4: At completion of recovery. At the end of procedures, the infusion of medications was discontinued to allow recovery of patients using Steward recovery score of 6.[14] The patients were monitored and maintained on oxygen until fully awake and then transferred to postanesthetic care unit (PACU) with fully monitoring. The postoperative nausea and vomiting were treated with ondansetron. Patients were discharged from the PACU to the pediatric Intensive Care Unit (ICU) according to modified Aldrete scoring system.[15] At the end of the procedure, the attending cardiologist was asked to document his satisfaction about anesthesia during the whole procedure using a scale of 10.

Outcomes

The primary outcome was the stability of the hemodynamic status of the patient and immobility during the procedure assessed by satisfaction by the cardiologist.

Secondary outcomes were induction time (IT), recovery time, and time needed in the PACU. The safety of the procedure was assessed by the occurrence of any adverse event.

Statistical analysis

Statistical analysis was performed by a person unaware of which group is which. Data were statistically described in terms of mean ± standard deviation (± SD) or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student's *t*-test for independent samples. For comparing categorical data, Chi-square (χ^2) test was performed. Fisher's exact test was used instead when the expected frequency is <5. $P < 0.05$ was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

The average of the multiple readings of heart rate, mean arterial blood pressure, respiratory rate, arterial partial pressure of carbon dioxide, arterial oxygen saturation, and temperature during the procedure was expressed as mean ± SD. There were no significant differences in these hemodynamic parameters regarding the baseline demographic data in each group ($P > 0.05$) [Table 1]. There was no difference regarding demographic data (age, sex, and weight) between both groups as shown in Table 1. The onset of sedation ("IT") was more rapid in ketofol group than in propofol group ($P = 0.0001$) [Figure 1]. There was

no significant difference in the UMSS between the two groups throughout the different time points of sedation. Table 2 demonstrates that there was no statistically significant difference between the two groups regarding the mean hemodynamic parameters during the procedure. The mean arterial blood pressure dropped by more than 20% of the baseline reading in three patients of propofol group and two patients of ketofol group during the procedure and managed with bolus doses (10-20 μg) of phenylephrine and fluids (P = 0.6). In propofol group, two patients developed desaturation below 90% for only 2–3 min and managed by repositioning the head and oxygen mask. There was no desaturation in ketofol group. There was no significant difference in the mean duration of the procedures between

Table 1: Baseline characteristics of the patients in both groups

Item	Group A (propofol) (n=30)	Group B (ketofol) (n=30)
Age (year)	14.48±1.26	14.09±1.32
Gender (female/male)	14/16	17/13
Weight (kg)	52.93±7.12	52±7.41
Heart rate (bpm)	79.9±7.5	79.0±6.9
MAP (mmHg)	85.3±6.9	85.1±6.6
Respiratory rate	15.7±2.2	14.9±2.1
$PaCO_2$ (mmHg)	37.4±2.3	37.9±2.9
SpO_2 (%)	97.6±2.1	97.7±2.2
Temperature (°C)	37.03±0.2	37.05±0.3

No significance difference between both groups, SPO_2: Arterial oxygen saturation, $PaCO_2$: Arterial tension of carbon dioxide, MAP: Mean arterial blood pressure

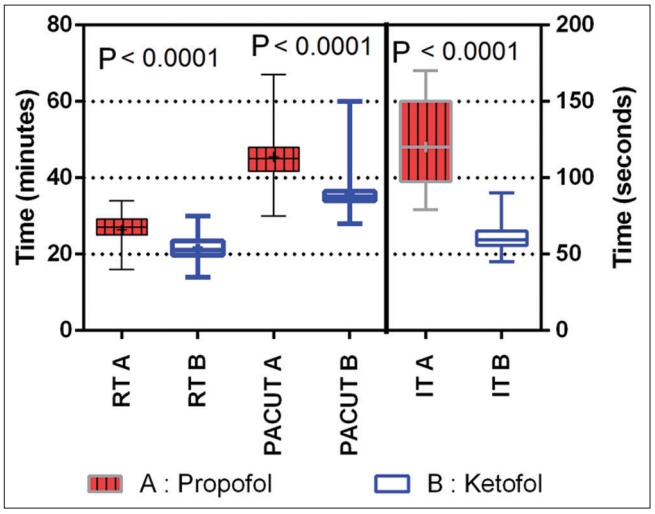

Figure 1: Time comparison of patients. IT: Induction time, RT: Recovery time, PACU: Postanesthesia care unit

Table 2: Intraoperative and postoperative data of patients

Item	Group A (propofol) (n=30)	Group B (ketofol) (n=30)	95% CI	P
Heart rate (bpm)	79.9±7.5	79.0±6.9	−4.681-2.881	0.6
MAP (mmHg)	85.3±6.9	85.1±6.6	−3.686-3.286	0.9
Respiratory rate (breath/min)	15.7±2.2	14.9±2.1	−1.917-0.3172	0.2
$PaCO_2$ (mmHg)	37.4±2.3	37.9±2.9	−0.9186-1.785	0.5
SpO_2 (%)	97.6±2.1	97.7±2.2	−1.017-1.217	0.9
Temperature (°C)	37.03±0.2	37.05±0.3	−0.09719-0.1439	0.7
Induction time (min)	120.2±28.5	60.3±9.0	−70.82-−48.98	0.0001
Michigan Sedation Score				
T0	0.21±0.38	0.20±0.41		0.751
T1	2,20±0.41	2.36±0.49		0.362
T2	2.19±0.43	2.20±0.40		0.845
T3	1.47±0.51	1.29±0.47		0.333
T4	0.33±0.48	0.27±0.45		0.702
Hypotension (n)	3	2	0.2407-10.05	0.6
Oxygen desaturation <90%	2	0	0.01-4.1	0.5
Duration of procedure (min)	135.67±32.67	133.67±31.62	−18.62-14.62	0.8
Cardiologist satisfaction	9.5±0.6	9.5±0.6	−0.2818-0.3163	0.9
Recovery time (min)	26.3±4.1	21.4±3.7	−6.936-−2.864	0.0001
Total fentanyl (μg)	171.23±26.6	151.49±28.2	−33.78-−5.699	0.0007
Total propofol (mg)	175.33±43.89	101.67±27.72	54.69-92.63	0.0001
Total ketamine (mg)	0	101.67±27.72		
Ondansetron	8	2	0.98-26.44	0.04
Duration in PACU (min)	45.5±6.8	35.8±4.5	6.453-12.88	0.0001
Modified Aldrete score	9.03±0.8	8.9±0.8	−0.5271-0.2604	0.5

Data are presented as mean±SD, number. CI: Confidence of interval, MAP: Mean arterial blood pressure, SPO_2: Arterial oxygen saturation, $PaCO_2$: Arterial tension of carbon dioxide, Michigan Sedation Score: University Michigan Sedation Score, PACU: Postanesthesia care unit, SD: Standard deviation

the two groups (P = 0.9). Patients were immobile during the whole procedure with excellent cardiology satisfaction with a mean score of 9.5 in both groups. The recovery time (duration from the end of procedures until the patients become fully awake) was longer in propofol group than the ketofol group (P = 0.0001) [Figure 1]. The total propofol added to ketofol was lower in the ketofol group than the propofol group patients (P = 0.001). The total fentanyl requirements during the procedures increased in patients of propofol group more than the ketofol group (P = 0.0007) [Table 2 and Figure 2]. The need for postoperative antiemetic drugs (ondansetron) in the PACU increased in patients of propofol group more than the ketofol group with a significant statistical difference (P = 0.04**).** The postoperative duration in the PACU until the patients were ready for discharge to the pediatric ICU was more prolonged in propofol group than the ketofol group (P = 0.001) [Figure 1]. There was no significant difference in the salivation in both groups. There was no significant difference in modified Aldrete score between the two groups (P = 0.5).

Discussion

The current study is the first to describe conscious sedation in a specific population with the same transcatheter interventional procedure. It is also the first to describe conscious sedation in the high-risk procedure of TPVI.

We used two regimens in conscious sedation to assess the safety of the procedure of conscious sedation and to compare both regimens to reach the ideal regimen for conscious sedation. Previous authors used variable regimens in conscious sedation during cardiac catheterization.[3-11]

Both types of sedation gained the cardiologist satisfaction during the procedure. Patients remained immobile and dynamically stable providing suitable environment for the interventionist to do his job without interruption or worries. The American Academy of Pediatrics stated that the aims of anesthesia in the cardiac catheterization laboratory are to provide analgesia, sedation, and anesthesia for patients, to maintain airway patency, to provide ventilation if needed, and to optimize the hemodynamic status before, during, and after the procedure.[1] We reported that both regimens of conscious sedation did the job according this statement.

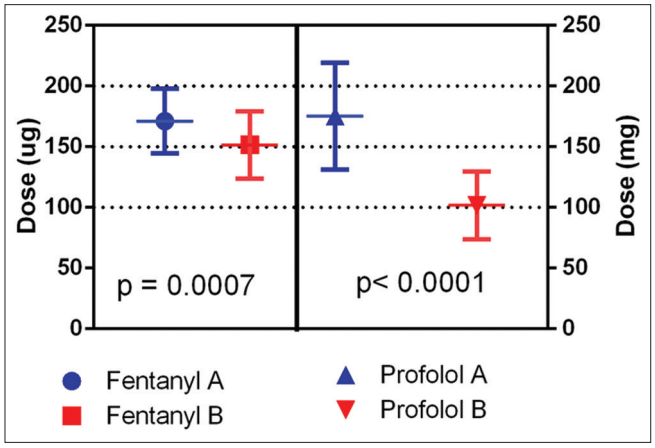

Figure 2: Total propofol and fentanyl doses of patients

In each group, patients remain hemodynamically stable with no significant difference between the baseline hemodynamic parameters and mean readings during the procedure. Furthermore, there was no difference in these parameters between both groups during the procedure. The mean arterial pressure (MAP) dropped below 20% in three patients in propofol group and two patients in the ketofol group without statistical significance. The blood pressure, heart rate, and systemic vascular resistance and combination of both minimize the changes in the hemodynamics during pediatric cardiac catheterization.[7,9]

Some studies found that the MAP and heart rate decreased significantly in propofol group than the ketofol group[7,16,17] while others found that heart rate and MAP decreased in patients receiving ketofol mixture for sedation.[5]

The arterial oxygen saturation dropped below 90% in two patients of propofol group due to attack of apnea and upper airway obstruction, and there was no any desaturation in ketofol group patients, and the same findings were also reported previously by Akin *et al*.[7] They assumed that adding ketamine to propofol infusion helps preserve respiratory function and upper airway control. Hui *et al*. found that adding ketamine did not prevent the apnea of propofol,[18] and David and Shipp found that the incidence of respiratory depression was similar between the propofol and ketofol.[17]

In our series of patients, although IT is more rapid in ketofol group, there is no difference regarding the sedation level using the UMSS. David and Shipp found that sedation scores were better in the ketofol group.[17] The total fentanyl dose was higher in propofol group than ketofol group, and this is due to the analgesic effect of ketamine in ketofol group. Previous studies showed that the potent analgesic effect of ketamine decreases the need for, and thus the potential risks of, coadministered opioids.[19,20] Akin *et al*.[7] found that total fentanyl doses were more in propofol group than ketofol group but did not reach significant difference (P = 0.057).

Although propofol has an antiemetic effect, the number of patients' required postoperative antiemetic medications in the PACU was higher in propofol group than ketofol group patients. This can be explained by the higher dose of fentanyl used in such group. Willman and Andolfatto found no incidence of nausea or vomiting in both groups.[21]

There was no significant difference regarding the duration of procedures between the patients of the two groups, but the recovery time was longer in propofol group, and this may be attributed to the increased dose of fentanyl. Previous studies showed either no difference in recovery

time or it is shorter in the ketamine group similar to our results.[7,9] Patients in the propofol group also required a longer duration in the PACU before being ready for discharge to the pediatric ICU.

The present study has some limitations as there was no blinding during anesthesia, so a double-blind protocol could not be applied and done in a single center.

Conclusion

Conscious sedation with either propofol or ketofol is effective and safe during TPVI. No difference in hemodynamic stability between both regimens. Ketofol has some advantages over the propofol as rapid IT, rapid RT, reduction of required narcotic dose, decreased incidence of postoperative nausea and vomiting, and a shorter stay in the PACU.

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Conflicts of interest

There are no conflicts of interest.

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