Original Research Article

Comparison of the combination of Propofol and Tramadol vs Propofol and Ketamine for intracavitary brachytherapy in cervical cancer

Minoti Baruah[1*], Tridip Jyoti Borah[2]

[1]Department of Anesthesiology, Critical Care & Pain, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India
[2]Department of Anesthesiology, Critical Care & Pain, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India

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Abstract

Background: Numerous combinations of drugs are used for sedation in intracavitary brachytherapy in cervical cancer. Objective of the study was to compare the combination of Propofol and Tramadol vs Propofol and Ketamine for intracavitary brachytherapy in cervical cancer. **Methods:** We performed a single-center randomized double blind controlled study in the Department of Anesthesiology, Dr. B. Borooah Cancer Institute, a tertiary cancer care center, Guwahati, Assam, India with 54 patients over a period of 3 months between December 2019 to February 2020. Variables like age, American Society of Anesthesiology score, Total time under sedation, Total dose of combination sedatives, Number of top up doses of combination sedatives, Pulse variation in study patients, Blood Pressure variation in study patients, Time taken to awakening in minutes by study patients, Time required for recovery in minutes by study patients and need for any emergent intervention were captured from study population. The study protocol was performed in accordance with the principles of the declaration of Helsinki and after approval by the Institutional ethical review board. A written informed consent was obtained from the eligible patients. Patients with history of allergy to any of the agents, eggs, soy were not included in the study. Also patients were excluded if they had ASA status greater than 3, had known hypersensitivity to either of the study products or were hemodynamically unstable. Eligible participants were randomized into either Propofol/Ketamine or Propofol/Tramadol group in a fixed 1:1 allocation from blocks of 4. The data was entered; tabulated and statistical analysis was performed by using Statistical Package for the Social Sciences (SPSS 24.0) and Graph Pad Prism Version 5. A value of $p<0.05$ was considered significant. **Results:** The mean age and median the study populations was 53.57 and 54.5 years (range, 26-74 years), respectively. Total dose of Propofol/Tramadol group and Propofol/Ketamine group was 21.035mL and 17.57 mL respectively. Total time required for awakening by patients receiving Propofol/Tramadol group and Propofol/Ketamine group was 2.13 mins and 4.45 mins, respectively. **Conclusion:** Propofol/Ketamine anesthesia in patients undergoing intracavitary brachytherapy in cervical cancer provided stable hemodynamic stability and sedation as compared to propofol/tramadol anesthesia.

Keywords: Ketamine, Propofol, Tramadol

Introduction

Intracavitary brachytherapy is now an established practice for carcinoma cervix [1]. An even increasing number of patients for the procedure has put a strain on the hospitalization and beds available, thus handling such patients on a day care basis benefits both hospitals and patients. The procedure required moderate to deep sedation and adequate analgesia to enable dilation of the cervical canal. A number of sedatives are currently used for the procedure including barbiturate, benzodiazepine, Propofol, Ketamine and opiods.

Procedural sedation and analgesia (PSA) in an important and growing field with a growing number of uses [2]. PSA gained widespread acceptance in human medicine after the development of computer controlled infusion devices that allow the depth of anesthesia to be altered as the same way it is altered during inhalation anesthesia. The primary goal of procedural sedation for patients in emergency care settings is to manage pain and anxiety while facilitating immediate interventional procedures. Unfortunately no sedative available today encompasses all these qualities, making combination of various drugs apparent to achieve these goals.

Propofol is regarded currently as the most suitable sedative for PSA.

*Correspondence
Dr. Minoti Baruah
Department of Anesthesiology, Critical Care & Pain, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India
E-mail: minotibaruah@gmail.com

It allows rapid changes in anaesthetic depth and a rapid clear-headed recovery.Propofol produces dose-dependent sedation, hypnosis, anxiolysis and amnesia as well as possessing antiemetic properties, but found to be weak analgesic and tends to depress hemodynamic parameters especially in patients with limited cardiovascular reserve and respiratory depression [3].Studies have shown that infusion of opioids in conjunction with propofol improves cardiovascular function, and enhances the quality of anesthesia recovery. Anesthesia based on opioids and nonopioid analgesics offers many clinical benefits, such as optimum hemodynamic stability, blocking response to surgical stress and capacity to reduce the required doses of other agents (either hypnotic or muscle relaxants). Ketamine is an N-methyl-D-aspartate receptor antagonist that induces a “dissociative state” in which sensory input (sight, hearing, touch) normally perceived by the patient is blocked from reaching consciousness. It is a unique anesthetic with profound analgesic, sedative, and amnestic properties and mostly used as an analgesic adjuvant to propofol in PSA regimens. But ketamine tends to stimulate hemodynamic parameters and may cause vomiting and unpleasant psychic reactions. Tramadol is a centrally acting analgesic which possesses opioid agonist properties and activates monoaminergic spinal inhibition of pain. It also inhibits the reuptake of norepinephrine and promotes the release of serotonin. The synergy of monoaminergic and opioid activity of tramadol achieves analgesic effects. Tramadol rarely causes respiratory or cardiovascular depression, even in large doses and this sets it apart from all other opioid agonists [4].

Considering these drug contrasting hemodynamic properties, the present study was undertaken to evaluate the combination of propofol/ketamine and propofol/tramadol in providing satisfactory

PSA towards intracavitary brachytherapy in cervical cancer in terms of hemodynamic parameters, analgesia, sedation and patient recovery.

Methods

We performed a single-center randomized double blind controlled study in the Department of Anaesthesiology, Dr. B. Borooah Cancer Institute, a tertiary care cancer center, Guwahati, Assam, India with 54 patients over a period of 3(three) months between December2019 to February 2020. Variables like age, American Society of Anesthesiology score, Total time under sedation, Total dose of combination sedatives, Number of top ups required of combination sedatives, Pulse variation in study patients, Blood Pressure variation in study patients, Time taken to awakening in minutes by study patients, Time required for recovery in minutes by study patients and need for any emergency intervention were captured from study population. The study protocol was performed in accordance with the principles of the declaration of Helsinki and after approval by the Institutional ethical review board. The study population was selected from adults (age range of 18 years to 65 years) who visited the tertiary care cancer center for day care intracavitary brachytherapy in cervical cancer. A written informed consent was obtained from the eligible patients. Patients with history of allergy to any of the agents, eggs, soy were not included in the study. Also patients were excluded if they had ASA status greater than 3, had known hypersensitivity to either of the study products or were hemodynamically unstable.

Eligible participants were randomized into either propofol/ketamine or propofol/tramadol group in a fixed 1:1 allocation from blocks of 4. Depending on randomization propofol/tramadol group had a 20 ml syringes prepared with tramadol 5mg/ml diluted with N/S and 20 ml syringes with 1% propofol. While propofol/ketamine group were given 20 ml syringes with ketamin diluted to 5 mg/ml and 20 ml syringes with 1% propofol.

Patients in propofol/tramadol group received 0.1 ml/kg IV of transparent syringes corresponding to 0.5 mg/kg tramadol and then 0.1 ml/kg IV of the white syringe (1 mg/kg propofol), while patients in propofol/ketamine group received the same IV volume 0.1 mg/kg of transparent syringe (0.5 mg/kg ketamine), and then 0.1ml/kg of opaque formulation. Medication from transparent syringe was injected as a bolus while white syringe injection was administered over 30 seconds and every dose guided by a weight specific schedule. Level of sedation was assessed using the Ramsay scale, if sedation was at sufficient depth, Ramsay scale >3 the procedure could be initiated. If sedation was judged inadequate a further dose of half the previous was injected. Top up doses were administered at half initial dose as required, till Ramsay score >3 was established and maintained.

Statistical analysis

The data was entered; tabulated and statistical analysis was performed by using Statistical Package for the Social Sciences (SPSS 24.0). Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. A value of $p<0.05$ was considered significant.

Results

During a period of 3 months between December 2019 to February 2020, 54 patients were enrolled in our study. Their mean and median age was 53.57 and 54.5 years (range, 26-74 years). Total dose of combination sedatives, number of top up of combination sedatives, Pulse variation in study patients, Blood Pressure variation in study patients, Total time taken by combination of sedatives, Time taken to awakening in minutes by study patients, Time required for recovery by study patients and need for any emergency intervention were captured from study population.

Table 1: Age Characteristics of the study population

Variables	Propofol/Tramadol group (N=28, 51.86%)	Propofol/Ketamine group (N=26, 48.14%)	P value
Age (years)			
Mean	53	54.19	0.52
Median	53.5	56	0.69
Range	30-74	26-74	NA

Age Characteristics of the study population are given in above Table 1. Mean age of study population belonging to Propofol/Tramadol group and Propofol/Ketamine group was 53 years and 54.19 years, respectively. Range of age variable was comparatively wider in Propofol/Ketamine group as compared to Propofol/Tramadol group.

Table 2: Characteristics of the study population as per ASA scoring

ASA score	Propofol/Tramadol group (N=28, 51.86%)	Propofol/Ketamine group (N=26, 48.14%)	P value
I	5 (17.85%)	7 (26.92%)	0.35
II	15 (53.57%)	12 (46.15%)	0.67
III	8 (28.57%)	7 (26.92%)	0.13

Characteristics of the study population as per ASA scoring are given in above Table 2. There was no statistically significant difference between Propofol/Tramadol group and Propofol/Ketamine group for each of the ASA score (ASA score I, II and III)

Table 3: Characteristics of the study population as per cardiac status

Cardiac status parameters	Propofol/Tramadol group (N=28, 51.86%)	Propofol/Ketamine group (N=26, 48.14%)	P value
Pulse variation (>20% of baseline)			
Yes	13 (46.42%)	8 (30.76%)	0.01
No	14 (50.00%)	18 (69.24%)	0.05
Not available	1 (3.58%)	0 (00.00%)	0.01
Blood Pressure variation (>20% from baseline)			
Yes	23 (82.14%)	2 (7.69%)	0.03
No	5 (17.86%)	24 (92.31%)	0.02
Need for any emergency	No	No	NA

Characteristics of the study population as per cardiac status are given in above Table 3.Our study observed statistically significant difference between Propofol/Tramadol group and Propofol/Ketamine group for both the cardiac status parameters [Pulse variation (>20%) and Blood

Pressure variation (>20%)]. Further, no patient population from either Propofol/Tramadol group and Propofol/Ketamine group required any emergency intervention.

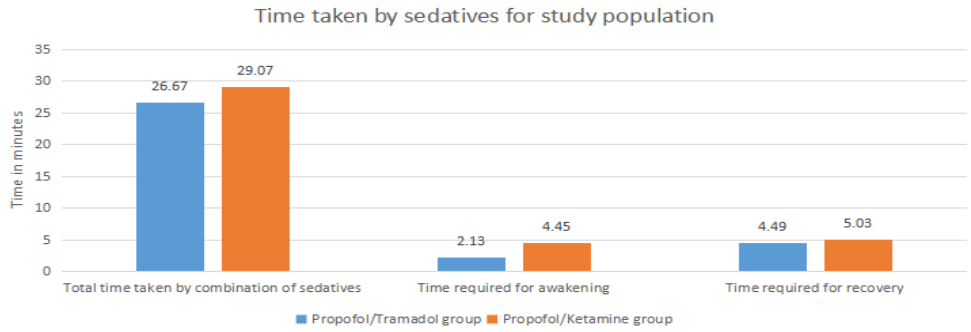

Fig 1: Time taken by combination of sedatives for study population

Time taken by combination of sedatives for study population is depicted in above Figure 1. Total dose of Propofol/Tramadol group and Propofol/Ketamine group was 21.035mL and 17.57 mL respectively. Total time required for awakening by patients receiving Propofol/Tramadol group and Propofol/Ketamine group was 2.13 mins and 4.45 mins, respectively. Whereas, time required for recovery by patients receiving Propofol/Tramadol group and Propofol /Ketamine group was 4.49 mins and 5.03 mins, respectively.

Discussion

Hemodynamic changes due to anesthesia in various surgeries have become a great concern in physicians operation room and evidence shows that changes in blood pressure, either increase or decrease, independently are associated with side effects and complications in patients undergoing any intervention [5-8]. During anesthesia, most patients experience periods of hemodynamic instability, which healthy individuals can tolerate, but are usually catastrophic in hypertensive patients due to the wide pressure fluctuations and sympathetic hyperactivity [9, 10]. PSA with propofol is similar to inhaled anaesthetics with regard to hemodynamic stability, emergence times, extubation times, early cognitive function, and adverse events. Propofol potentiates GABAA receptor activity, has a rapid onset of action and it is very short acting. It has a neuroprotective effect during cerebral ischemia, lowering intracranial pressure, cerebral blood flow, cerebral metabolism and oedema, and improving cerebral perfusion pressure and mean arterial pressure (MAP) [11, 12].However, propofol has a narrow therapeutic index and lacks intrinsic analgesic properties. Patients generally receive a combination of anesthetic and analgesic agents to induce and maintain an adequate depth of anesthesia and analgesia. Traditional opioids produce analgesia but also cause constipation, respiratory depression, and sedation, as well as having a significant abuse potential. Studies have shown that non-opioid drug combination produced adequate anesthesia with less cardiovascular stimulation and rapid recovery compared to opiate induced anesthesia [5-7].In this study, the effect of two different anesthetic techniques, i.e., propofol/ketamine and propofol/tramadol for induction of anesthesia on hemodynamic variables were compared in patients undergoing intracavitary brachytherapy in cervical cancer. PSA with both techniques is comparable, but propofol and tramadol combination may be considered an appropriate choice when hemodynamic stability is of great importance especially in hypertensive patients [13, 14]. Blood pressure variations under propofol/ketamine anesthesia were minimal compared with propofol/tramadol anesthesia. Studies showed a significant decrease in Pulse variation and Blood Pressure variation after induction with propofol/ketamine anesthesia. The decrease in Pulse variation and Blood Pressure variation with propofol/ketamine anesthesia may be due to fact that ketamine has no clinically relevant hemodynamic effects [15]. Studies have shown that tramadol rarely causes cardiovascular depression, even in large doses and this sets it apart from all other opioid agonists [15]. Tramadol is as effective as and safer than equianalgesic doses of opiates because it has been associated with less sedation, cardiovascular effects, which are favourable for sedation in patients undergoing intracavitary brachytherapy in cervical cancer [16].

Our study has some limitations. First, we do not know whether patients experienced unpleasant dreams and hallucinations after the procedures, and we have not captured any side effects of the study agents.

Conclusion

In conclusion, the results of this study suggest that both propofol/ ketamine and propofol/tramadol combinations produced stable hemodynamics and adequate sedation, in patients undergoing brachytherapy. These combinations provided rapid, pleasant and safe anesthesia with minor hemodynamic fluctuations. There were no adverse hemodynamic changes from induction until the end of our investigation. Additional studies using a larger group of patients are warranted to detect the small but potentially clinically significant differences between the two groups.

Ethical approval

The study was approved by the Institutional Ethics Committee

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