Original Research Article

Change in Requirement of Propofol During Subsequent Sessions of Intracavitary Brachytherapy Applications

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Abstract

Cancer cervix patients need intracavitary brachytherapy as a treatment modality for which sedation is needed. Usually each patient requires 4 cycles. Propofol dose requirement was studied in subsequent cycles to see any increase in dose as the cycle progresses. **Materials and Methods:** After approval of the hospital ethical committee, 60 American Society of Anaesthesiology (ASA) I and II patients were studied for change in their haemodynamic variables and Propofol doses to maintain the sedation level at Modified Ramsay Sedation Score (MRSS) of 8 which is required for brachytherapy procedure. **Results:** There was no statistically significant change in a haemodynamic variables over subsequent cycles. The Propofol doses initially decreased but then increased to near previous doses only to maintain MRSS of 8. **Conclusion:** On the basis of present study we concluded that average Propofol doses did not increase in subsequent cycles to maintain the appropriate sedation level for the procedure.

Keywords: Propofol, Tolerance, Haemodynamic Changes, Intracavitary Brachytherapy.

Introduction

Aim

To evaluate change in Propofol dose requirement over subsequent brachytherapy cycles in cancer cervix patients.

Objective

- To assess the change in dose of Propofol during subsequent sessions of intracavitary brachytherapy.
- To assess the level of sedation with Propofol during and after the procedure.

Sedation is frequently required for patients with cancer of cervix while they undergo intracavitary brachytherapy where brachytherapy applicators are inserted in uterine cavity and vaginal packing is done. Various drugs are used for sedation Propofol is among the most common sedative & hypnotic drug being used. Since, in present study patient needed repeated sedation with Propofol weekly, we studied how the requirement of Propofol changed during subsequent sessions to assess the development of tolerance to Propofol.

Drug tolerance can be defined as progressively diminished response to a drug with repeated exposure. Development of tolerance to drugs that depress the Central Nervous System (CNS) is commonly seen. Pharmacologic tolerance has been observed with ethanol, sedatives / hypnotics, opioids, nitrous oxide[1-3] and anti anxiety agents.

Two types of tolerance are generally seen. Pharmacokinetic and Pharmacodynamic[1]. Pharmacokinetic tolerance results from a change in the absorption, distribution, metabolism or excretion of a drug that effectively reduces the concentration of that drug at its receptors. Pharmacodynamic tolerance results from adaptive changes within the patient so that the response to a given concentration of drug is reduced. This involves usually up regulation of the receptor or change in drug receptor number and the amount of tolerance can vary from small changes to major changes. Tolerance is described as a complex process in which both mechanisms may contribute Ketamine tolerance has been reported in both burn and radiotherapy patients after repeated exposure to it[4-7] although different mechanism is involved in development of tolerance to it.

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Materials and methods:-

After taking approval of the hospital ethical committee and written informed consent the study was started-

Study design - Prospective observational study

Study area - Chirayu Medical College & Hospital (Tertiary centre of M.P)

Sample size - 60 patients (American Society of Anaesthesiology (ASA) grade-I and II)

Study period - January 2020 to January 2021

Inclusion criteria

- ASA grade I and II
- Age between 45-65 years.
- Cancer cervix patients scheduled for intracavitary brachytherapy.

Exclusion criteria

- ASA grade III and IV patients
- Patient requiring > 4 cycles

- Who did not give consent to be a part of study
- Patients in whom procedures lasted for >30 minutes
- Allergy to egg protein.

Data Collection

After confirming Nil per Oral (N.P.O) status, Patients were shifted to Operation Theater (OT). Intravenous (I.V) line secured and monitors were attached and Heart Rate (HR), Blood Pressure (BP), Oxygen Saturation (SPO_2), Respiratory Rate (RR) were recorded. The haemodynamic parameters were recorded at following times. Baseline, at induction, and at following minutes after induction –
5 minutes
10 minutes
15 minutes
20 minutes

The procedure usually lasted for 20-30 minutes. All the procedures were done by same radiation oncologist to remove any bias occurring due to procedure technique & time duration. Following drugs were given I.V. Glycopyrolate 0.2mg, I.V. Midazolam 1 mg, I.V. Fentanyl 1mcg/kg, I.V. Propofol 1mg/kg. Slowly in small aliquots to avoid any respiratory compromise. Intra-operatively sedation level was assessed by using MRSS.

Modified Ramsay Sedation Score (MRSS) score

Score	Definition
1.	Awake and alert, minimal or no cognitive impairment
2.	Awake but tranquil, purposeful responses to verbal commands at conversation level
3.	Appears asleep, purposeful responses to verbal commands at conversation level.
4.	Appears asleep, purposeful response to verbal commands but at louder than usual conversation level or requiring light glabellar tap
5.	Asleep, sluggish purposeful responses only to loud verbal commands or strong glabellar tap
6.	Asleep, sluggish purposeful responses only to painful stimuli
7.	Asleep, reflex withdrawal to painful stimuli only (no purposeful response)
8.	Unresponsive to external stimuli, including pain

When the patient reached MRSS of 8, procedure was started and was maintained at same level throughout the procedure. If MRSS was < 8 then additional Propofol doses were given. These additional doses of Propofol were then compared in subsequent cycles. Immediately after the procedure modified MRSS was noted then the MRSS was noted 15minutes after the procedure.

Statistical analysis

Qualitative data were expressed by using frequency & percentages. Data entry done in Microsoft Excel and appropriate chisquare test were applied as and when required. "P" value <0.05 was considered as significant.

Result

Table 1: Patient's Characteristic

Characteristics	All patients (n=60)
Age (in years)	52.15 ± 8.60
Weight (kg)	56.9 ± 4.90

Table 2: Duration of procedure

Duration of procedure (in minute)		Total number of patients (N)	Mean	Std. Deviation	P value
	Cycle I	60.00	29.25	1.80	<0.001
	Cycle II	60.00	25.92	1.95	
	Cycle III	60.00	26.08	2.08	
	Cycle IV	60.00	26.08	2.08	

The mean Baseline Heart Rate (HR) among all 4 cycles varied between 74.18 to 80.63 beats per minutes.
In cycle I the mean HR at induction and at various intervals after induction varied between 75.87 to 83.58 beats per minutes.
In cycle II the mean HR at induction and at various intervals after induction varied between 75 to 81.45 beats per minutes.
In cycle III the mean HR at induction and at various intervals after induction varied between 72.68 to 80.63 beats per minutes.
In cycle IV the mean HR at induction and at various intervals after induction varied between 71.98 to 83.35 beats per minute.
Mean baseline Systolic Blood pressure (SBP) among all four cycles varied between 137.08 to 140.67 mmHg.
In cycle I SBP at induction and at various intervals after induction varied between 131.77 to 134.50 mmHg.
In cycle II SBP at induction and at various intervals after induction varied between 138.17 to 132.15 mmHg.
In cycle III SBP at induction and at various intervals after induction varied between 138.82 to 134.05 mmHg.
In cycle IV SBP at induction and at various intervals after induction varied between 139.93 to 144.57 mmHg.

Baseline mean Diastolic Blood Pressure (DBP) among all 4 cycles varied between 77.82to 79.78 mmHg.
In cycle I DBP at induction and at various intervals after induction mean DBP varied between 76.98 to 79.10 mmHg.
In cycle II DBP at induction and at various intervals after induction mean DBP varied between 77.72 to 79.88 mmHg.
In cycle III DBP at induction and at various intervals after induction mean DBP varied between 78.05 to 78.55 mmHg.
In cycle IV DBP at induction and at various intervals after induction mean DBP varied between 76.98 to 81.75 mmHg.

Baseline mean Respiratory Rate (RR) among all 4 cycles varied between 16.02 per minutes to 16.83 per minutes.
In cycle I mean RR at induction and at various intervals after induction varied between 15.87 to 14.33 per minutes.
In cycle II mean RR at induction and at various intervals after induction varied between 13.77 to 16.15 per minutes.
In cycle III mean RR at induction and at various intervals after induction varied between 13.77 to 16.07 per minutes.
In cycle IV mean RR at induction and at various intervals after induction varied between 14.22 to 16.88 per minutes.
All the haemodynamic variables including the baseline parameters, at induction and at various intervals after induction did not change significantly and were comparable.

Table 3: MRSS immediately after Procedure

MRSS immediately after the procedure		N	Mean	Std. Deviation	P value
	Cycle I	60.00	3.50	.50	.001
	Cycle II	60.00	3.42	.50	
	Cycle III	60.00	3.38	.49	
	Cycle IV	60.00	3.70	.46	
	Total	240.00	3.50	.50	

Table 4: MRSS 15 Minutes after Procedure

MRSS 15 Minutes after the procedure		N	Mean	Std. Deviation	P value
	Cycle I	60.00	1.48	.50	<0.001
	Cycle II	60.00	1.35	.48	
	Cycle III	60.00	1.32	.47	
	Cycle IV	60.00	1.85	.36	
	Total	240.00	1.50	.50	

Table 5: Additional Propofol dose

Additional Propofol dose		N	Mean	Std. Deviation	P value
	Cycle I	60.00	32.67	7.33	.484
	Cycle II	60.00	30.67	8.80	
	Cycle III	60.00	31.50	8.40	
	Cycle IV	60.00	32.17	10.43	
	Total	240.00	31.75	8.79	

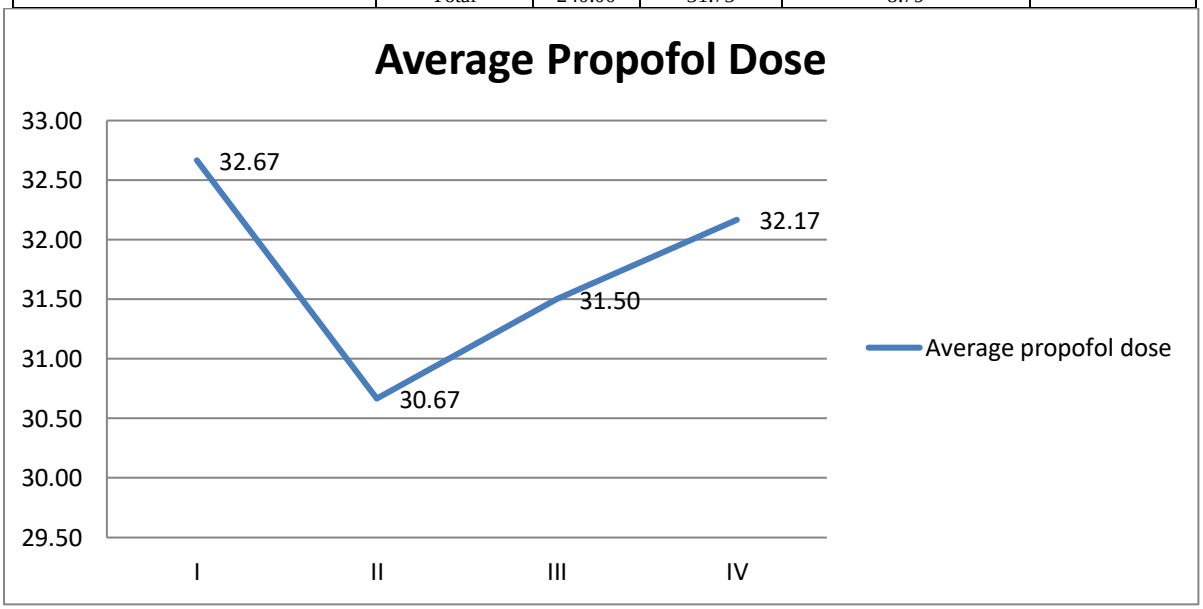

Fig. 1: Number of cycles and Propofol doses (in mg)

Discussion

In this prospective study, we demonstrated that requirement of Propofol was not significantly changed over the successive brachytherapy cycles also there was no definite pattern in change of Propofol dose over subsequent cycles. Thus based on our findings we did not find any increase in dose requirement over the entire treatment period.

The study done by Setlock MA et al[8] included a small number of children (n=6) and used other hypnotics in conjunction with Propofol hence they failed to exclude the possibility of interaction between Propofol and other anaesthetics but in our study the sample size was 60 patients and no other hypnotic was used to cause synergistic effect.

Study done by S. Buehrer et al[9] used a fixed dose rate for Propofol after sufficient depth of sedation was obtained but in our study we used small aliquots of Propofol to achieve MRSS of 8 after a initial dose of 1 mg/kg and and hence there was no incidence of desaturation and airway complications also post procedure patients were arousable as dose was individualized.

Sokya M, Fisher et al[10] also concluded in their study that tolerance did not appear to develop after repeated administration although it was a retrospective study and lacked in having a systematic dosing scheme in contrast to our study which is a prospective study and dosing scheme is systematic.

Study done by RyungA Karg et al[11] had general limitation as it used Richmond Agitation- Sedation Scale (RAAS) score to assess depth of sedation by three different anaesthesiologist which increase the risk of inter -observer bias but our study used MRSS to maintain and monitor depth of sedation by one anaesthesiologist only eliminating inter -observer bias.

Shaikh N et al[12] evaluated the development of tolerance to Propofol in a similar study which was also a retrospective study and sample size was small (24 patients) as compared to 60 sample size in the present study. They also concluded that repeated administrations

of Propofol at time intervals do not lead to the development of tolerance.

Study limitation

In the present study Propofol requirement for the various cycles did not change significantly for the study subjects as initially the average dose decreased for Propofol but later in cycle III and IV the dose started to increase but could not reach at cycle I level. Hence no clear trend was seen based on present study we can say that more cycles would be needed to see tolerance to Propofol.

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