Original Research Article

Dexmedetomidine versus propofol for attenuation of hemodynamic response to creation of pneumoperitoneum in laparoscopic cholecystectomies: A randomised prospective study

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Abstract

Background: Creation of pneumoperitoneum has been found to be associated with hemodynamic changes and hence various drugs have been studied to attenuate such response. **Aims:** To compare the effectiveness of dexmedetomidine and propofol in attenuating the hemodynamic response to pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. **Materials and methods:** Eighty patients of American Society of Anaesthesiologists (ASA) physical status I or II were randomly allocated into two groups to receive dexmedetomidine or propofol infusion after induction of anaesthesia. Hemodynamic parameters (heart rate, Systolic and diastolic blood pressure), duration of pneumoperitoneum, time to extubation were recorded. Statistical analysis was done using students t test and chi-square test and p value<0.05 was considered significant. **Results:** Both dexmedetomidine and propofol attenuated the hemodynamic response to pneumoperitoneum, but heart rate and systolic blood pressure showed better control in dexmedetomidine group, whereas diastolic blood pressure was comparable between two groups. Total duration of pneumoperitoneum and time to extubation were comparable between the two groups. **Conclusion:** Dexmedetomidine infusion without loading dose is effective in preventing hemodynamic response to pneumoperitoneum in patients undergoing laparoscopic cholecystectomy and may be better alternative to propofol in such patients.
Key Word: Dexmedetomidine, pneumoperitoneum, hemodynamic response.

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INTRODUCTION

Laparoscopic cholecystectomy has become gold standard surgery for cholelithiasis[1] Advantages of laparoscopic cholecystectomy are shorter hospital stay, early ambulation, smaller scar, and less compromised postoperative respiratory and gastro-intestinal functions. However, the procedure is not risk free as it is associated with significant hemodynamic changes due to creation of pneumoperitoneum, potential for systemic absorption of carbon dioxide, and reverse Trendelenberg position[2] Increase in heart rate and blood pressure in response to pneumoperitoneum produced during laparoscopic cholecystectomy is a challenging situation for a practising anaesthesiologist[3,4] Without adequate control of sympathetic response there is a chance of increase in morbidity of the patient during the perioperative period hampering the speedy recovery of the patient. Many

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drugs including nitroglycerine, β blocker, and opioids are used to provide hemodynamic stability during pneumoperitoneum,[5,6] but they have their own disadvantages. Dexmedetomidine is a selective α2 agonist with central sympatholytic properties. Intravenous use of dexmedetomidine in the perioperative period had been found to decrease serum catecholamine levels by 90%, to blunt the haemodynamic response to laryngoscopy, tracheal intubation, to provide sedation without respiratory depression and to decrease post-operative analgesic requirements.[7,8] Dexmedetomidine, by virtue of its central sympatholytic effect should be able to attenuate the sympathetic response to pneumoperitoneum. Propofol allows for a rapid induction and recovery from anaesthesia, as well as good haemodynamic maintenance when used during the intraoperative period.[8] It produces its anaesthetic effect by positive regulation of GABA, an inhibitory neurotransmitter through ligand gated $GABA_A$ receptors. We designed this study to compare the effectiveness of dexmedetomidine in attenuating the hemodynamic response to pneumoperitoneum using only the maintenance dose (0.2-0.7 μg/kg/hr) with that of propofol (25-75 μg/kg/hr) infusion.

MATERIALS AND METHODS

This prospective, randomised study was done in a tertiary care institute in India. Written informed consent was taken before enrolling the patient into the study. 80 ASA I and II patients undergoing laparoscopic cholecystectomy under general anesthesia between the ages of 20 and 50 years of both sexes were randomly divided into two groups of 40 patients each using a sealed envelope method, with Group D to receive dexmedetomidine infusion and Group P to receive propofol infusion. A preanaesthetic check up was done one day prior to surgery. Patients with history of allergy to the study drugs, uncontrolled diabetes and hypertension, pregnant females and those with deranged liver function test were not included in the study. Patients where conversion to open cholecystectomy was done were also excluded from the study. On arrival to the operating room, a 20 G intravenous line was secured and after applying standard monitoring device (non invasive blood pressure, electro cardiogram, percent saturation of arterial oxygen, end tidal carbon dioxide monitor) and premedication with injection glycopyrrolate 0.01 $mg.kg^{-1}$ to reduce airway secretions, all patients were induced with 3 $mg.kg^{-1}$ bodyweight of sodium thiopentone and airway secured with appropriate sized endotracheal tube after giving injection fentanyl 2 $\mu g.kg^{-1}$ and injection Atracurium 0.5 $mg.kg^{-1}$. Anaesthesia was maintained with a mixture of oxygen and nitrous oxide in 50:50 ratio and isoflurane to maintain a minimum alveolar concentration of 1.0. Muscle relaxation throughout surgery was maintained by bolus doses of atracurium. Group D received injection dexmedetomidine infusion (diluted with 24 mL of preservative free normal saline to achieve a dilution of $4\mu g.mL^{-1}$) in a dose range of 0.2 to 0.7 $\mu g.kg^{-1}.h^{-1}$ while Group P received injection propofol infusion in a dose range of 25-75 $\mu g.kg^{-1}.h^{-1}$. Both the drugs were started immediately after securing the airway and titrated to ensure heart rate and systolic blood pressure did not rise more than 30% of the pre pneumoperitoneum value. Titration was done by starting the drug at the midpoint of the dose range and titrated upwards or downwards depending on the increase or decrease in haemodynamic parameters respectively. The infusions of both the drugs were stopped at the end of pneumoperitoneum. Loading dose of dexmedetomidine was not given as per the study design. The intra abdominal pressure of pneumoperitoneum was kept constant at 12 mmHg. The study drugs could not be blinded from the anaesthesiologist performing the study in view of the physical nature of the drug (propofol being white in colour) and need to adjust the dosing as per clinical response. Haemodynamic parameters including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure(DBP) were noted just before establishing the pneumoperitoneum and every two minutes after establishing the pneumoperitoneum for the first 10 minutes and subsequently every 10 minutes till the end of pneumoperitoneum using an automated multi channel monitor. Increase in Systolic Blood Pressure (SBP) or Heart Rate (HR) to more than 30% of the pre pneumoperitoneum value even after the highest dose of infusion drugs was described as failure to control the haemodynamic response and was rescued with bolus dose of injection fentanyl $0.5\mu g.kg^{-1}$ and injection esmolol 10 mg bolus dose respectively. One patient in dexmedetomidine group and two patients in propofol group required conversion to open surgery due to technical difficulties and were excluded from the study. Hypotension was described as fall in SBP below 90 mmHg and treated with bolus dose of injection ephedrine 6 mg while bradycardia was described as fall in heart rate below 50 $beats.min^{-1}$ and treated with injection atropine 0.6 mg in divided dose. After the establishment of spontaneous respiration and reversal of residual effect of muscle relaxant by injection neostigmine 0.04 $mg.kg^{-1}$ and glycopyrolate 10 mcg/kg patients were extubated once they started responding. The data thus obtained was entered into computer using Microsoft Excel. Statistical analysis was done using students t test and chi-square test and p value<0.05 was considered significant.

RESULTS AND OBSERVATIONS

The groups were comparable with respect to age, weight, gender ratio and ASA status of patients [Table 1].

Table 1: Comparison of demographic parameters between two groups

Criterion	Group D n=39	Group P n = 38	p-value
Age (years)	36.33±11.08	40.43±12.71	0.135
Gender (M/F)	10/29	13/25	0.411
Weight (Kgs)	65.34±9.40	63.54±8.52	0.381
ASA (I/II)	30:9	29.9	0.949

Baseline mean HR in dexmedetomidine group was 89.74±9.57mmHg. After creation of pneumoperitoneum mean HR increased but the difference was not statistically significant (p value>0.05). Thereafter decrease in mean heart rate below baseline values was noted. Heart rate remained below baseline at rest of study stages with difference being significant in later study stages. Postoperative mean HR was also below baseline and was statistically significant [Table 2]. Baseline mean HR in propofol group was 85.43±11.02 mm Hg. At 2 min after pneumoperitoneum mean HR increased to 94.60± 7.60 mm Hg. This increase was statistically significant (p value<0.05). After than decrease in heart rate was seen at most of the study stages and remained comparable to baseline except at 60 min after pneumoperitoneum when heart rate was significantly below baseline (p value<0.05). Postoperative mean HR was 85.79 ± 7.89 which was comparable to baseline. [Table 3]

Table 2: Intra group comparison of mean heart rate (HR) in group D (Dexmedetomidine)

	Mean HR (beats/min) Group D n=39	P value	Remarks
Pre –op	89.74±9.57		
2 MIN	92.21±8.46	0.230	NS
4 MIN	88.60±7.12	0.552	NS
6 MIN	85.63±9.89	0.066	NS
8 MIN	88.80±5.89	0.602	NS
10 MIN	82.32±11.27	0.002	S
20 MIN	84.70±10.9	0.033	S
30 MIN	80.1±9.23	<0.0001	HS
40 MIN	76.23±9.0	<0.0001	HS
50 MIN	78.34±5.42	<0.0001	HS
60 MIN	78.76±10.34	<0.001	HS
POST OP	82.63±8.67	0.001	HS

NS-not significant, HS-highly significant

Table 3: Intragroup comparison of mean HR in Group P (Propofol)

	Mean HR (beats/min) Group P n=38	P value	Remarks
Pre –op	85.43±11.02		
2 MIN	94.60±7.60	0.0001	HS
4 MIN	86.21±5.64	0.702	NS
6 MIN	86.30±7.58	0.689	NS
8 MIN	87.11±6.23	0.418	NS
10 MIN	89.76±7.3	0.050	NS
20 MIN	82.33±10.11	0.205	NS
30 MIN	85.30±7.67	0.952	NS
40 MIN	83.90±12.03	0.564	NS
50 MIN	**82.84±7.4**	**0.232**	**NS**
60 MIN	**77.5±8.0**	**<0.001**	**HS**
POST OP	**85.79±7.89**	**0.870**	**NS**

NS-not significant, HS-highly significant

Intergroup comparison showed comparable baseline mean HR between the two groups. Although patients in the dexmedetomidine group had lower mean HR at most of study stages than patients in propofol group, the difference was not statistically significant (p value>0.05). There was a significant difference in postoperative mean HR between two groups with HR being lower in dexmedetomidine group [Table 4]. Baseline mean systolic blood pressure in dexmedetomidine group was 126.47±11.40 mm Hg. After creation of pneumoperitoneum, mean SBP increased to 134.21±10.76 mm Hg at 2 min and 128.50±13.45 mm Hg at 4 minutes and the difference was statistically significant.

Thereafter at rest of the study stages, mean SBP was lower than the baseline values with the difference being statistically significant from 10 minutes afterwards (p value<0.05). Post operative mean SBP (117.43±12.23 mm Hg) was also significantly lower than baseline SBP in this group [Table 5]. In the propofol group, baseline mean SBP was 123.8±10.7 mm Hg and at two min after pneumoperitoneum creation, mean SBP increased to 138. 86±9.90 mm Hg and the increase was statistically significant (p-value<0.05). SBP remained higher than baseline up to 10 minutes after pneumoperitoneum creation, although the difference was not statistically significant. Thereafter, lowering of systolic BP compared to baseline was seen. Postoperative SBP was 130.09±14.54 mm Hg which was significantly higher than baseline and p-value of <0.05 [Table 6]. Intergroup comparison shows comparable mean SBP at baseline between the two groups. At most of the study stages lower values of mean SBP were observed in the dexmedetomidine group, thus suggesting better control of SBP with dexmedetomidine compared to propofol. Postoperative mean SBP also showed better control in dexmedetomidine group as compared to propofol group [Table 7].

Table 4: Intergroup comparison of mean heart rate (HR) between two groups

	Mean HR(beats/min)		P – value	Remarks
	Group D n=39	Group P n=38		
Pre –op	89.74±9.57	85.43±11.02	0.070	NS
2 MIN	92.21±8.46	94.60±7.60	0.196	NS
4 MIN	88.60±7.12	86.21±5.64	0.106	NS
6 MIN	85.63±9.89	86.30±7.58	0.740	NS
8 MIN	88.80±5.89	87.11±6.23	0.225	NS
10 MIN	82.32±11.27	89.76±7.3	0.264	NS
20 MIN	84.70±10.9	82.33±10.11	0.326	NS
30 MIN	80.1±9.23	85.30±7.67	0.680	NS
40 MIN	76.23±9.0	83.90±12.03	0.174	NS
50 MIN	78.34±5.42	82.84±7.4	0.094	NS
60 MIN	78.76±10.34	77.5±8.0	0.004	NS
POST OP	82.63±8.67	85.79±7.89	0.655	NS

NS-not significant, HS-highly significant

Table 5: Intragroup comparison of systolic blood pressure (SBP)

	Mean SBP (mm HG)	P value	Remarks
	Group D n=39		
Pre –op	126.47±11.40		
2 MIN	134.21±10.76	0.003	S
4 MIN	128.50±13.45	0.476	NS
6 MIN	121.66±14.34	0.105	NS
8 MIN	117.98±7.4	0.000	NS
10 MIN	115.83±6.9	0.0001	S
20 MIN	112.14±13.9	0.0001	S
30 MIN	112.2±8.6	<0.0001	HS
40 MIN	110.76±9.4	<0.0001	HS
50 MIN	102.09±15.76	<0.0001	HS
60 MIN	104.6±10.33	<0.0001	HS
POST OP	117.43±12.23	0.001	HS

NS-not significant, HS-highly significant, S-significant

Table 6: Intragroup comparison of systolic blood pressure (SBP)

	Mean SBP (mm HG)	P value	Remarks
	Group P n=38		
Pre –op	123.80±10.7		
2 MIN	138.86±9.90	<0.0001	HS
4 MIN	128.48±11.98	0.069	NS
6 MIN	124.45±17.98	0.839	NS
8 MIN	124.23±11.90	0.865	NS
10 MIN	120.87±9.78	0.202	NS
20 MIN	118.64±16.3	0.101	NS
30 MIN	113.73±14.23	0.0007	HS

40 MIN	114.9±12.67	0.0011	HS
50 MIN	112.84±16.32	0.0007	HS
60 MIN	119.27±17.62	0.173	HS
POST OP	130.09±14.54	0.031	S

NS-not significant, HS-highly significant, S-significant

Table 7: Intergroup comparison of systolic blood pressure (SBP)

	Mean SBP(mm Hg)		P – value	Remarks
	Group D n=39	Group P n=38		
Pre –op	126.47±11.40	123.8±10.7	0.293	NS
2 MIN	134.21±10.76	138.86±9.90	0.0523	NS
4 MIN	128.50±13.45	128.48±11.98	0.9945	NS
6 MIN	121.66±14.34	124.45±17.98	0.453	NS
8 MIN	117.98±7.4	124.23±11.90	0.007	S
10 MIN	115.83±6.9	120.87±9.78	0.012	S
20 MIN	112.14±13.9	118.64±16.3	0.063	NS
30 MIN	112.2±8.6	113.73±14.23	0.621	NS
40 MIN	110.76±9.4	114.9±12.67	0.819	NS
50 MIN	102.09±15.76	112.84±16.32	0.0009	HS
60 MIN	104.6±10.33	119.27±17.62	<0.0001	HS
POST OP	117.43±12.23	130.09±14.54	<0.0001	HS

NS-not significant, HS-highly significant, S-significant

Baseline mean diastolic blood pressure in dexmedetomidine group was 73.10±10.26 mm Hg. After creation of pneumoperitoneum slight increase in mean diastolic blood pressure was seen, however the difference was not statistically significant (p value>0.05). DBP was lower than baseline at 10, 20 , 30 , 40 ,50 and 60 min after pneumoperitoneum and this difference was statistically significant (p value<0.05). Post operative DBP was also lower than baseline but the difference was not significant statistically [Table 8]. In propofol group baseline DBP was 74.1±8.64 mm Hg. Diastolic BP also increased slightly in comparison to baseline in this group (2 and 4 min after pneumoperitoneum), but the difference was not statistically significant (p value>0.05). Thereafter DBP was lower than baseline at rest of study sages with the difference being significant at 20 min after pneumoperitoneum and afterwards. Postoperative DBP was comparable to baseline with value of 74.6±6.88 and p-value >0.05 [Table 9]. Intergroup comparison shows comparable baseline DBP between two groups. A similar trend of DBP was observed win both groups with values being comparable at corresponding study stages except at 60 minutes where lower DBP was observed in the dexmedetomidine group and the difference was significant (p value<0.05). Postoperative DBP was comparable between two groups [Table 10].

Table 8: Intragroup comparison of diastolic blood pressure (DBP)

	Mean DBP (mm Hg) Group D n=39	P value	Remarks
Pre –op	73.12±10.26		
2 MIN	76.43±8.76	0.129	NS
4 MIN	74.72±6.99	0.423	NS
6 MIN	71.6±7.28	0.452	NS
8 MIN	74.02±7.28	0.656	NS
10 MIN	70.23±6.31	0.138	NS
20 MIN	68.60±5.86	0.019	S
30 MIN	66.52±4.12	0.000	HS
40 MIN	64.23±6.12	<0.0001	HS
50 MIN	63.33±4.21	<0.0001	HS
60 MIN	62.19±6.33	<0.0001	HS
POST OP	72.7±6.16	0.835	NS

NS-not significant, HS-highly significant, S-significant

Table 9: Intragroup comparison of diastolic blood pressure (DBP)

	Mean DBP (mm Hg) Group P n=38	P value	Remarks
Pre –op	74.31±8.64		
2 MIN	77.01±10.23	0.217	NS
4 MIN	76.5±7.15	0.232	NS
6 MIN	73.24±6.78	0.550	NS
8 MIN	72.62±5.27	0.306	NS
10 MIN	71.25±6.58	0.086	NS
20 MIN	68.90±7.66	0.005	S
30 MIN	67.91±5.82	0.000	HS
40 MIN	65.42±5.91	<0.0001	HS
50 MIN	63.81±5.76	<0.0001	HS
60 MIN	66.42±5.99	<0.0001	HS
POST OP	74.63±6.88	0.997	NS

NS-not significant, HS-highly significant, S-significant

Table 10: intergroup comparison of diastolic blood pressure (DBP)

	Mean DBP(mm Hg)		P – value
	Group D n=39	Group P n=38	
Pre –op	73.12±10.26	74.31±8.64	0.584
2 MIN	76.43±8.76	77.01±10.23	0.789
4 MIN	74.72±6.99	76.5±7.15	0.272
6 MIN	71.6±7.28	73.24±6.78	0.309
8 MIN	74.02±7.28	72.62±5.27	0.337
10 MIN	70.23±6.31	71.25±6.58	0.489
20 MIN	68.60±5.86	68.90±7.66	0.847
30 MIN	66.52±4.12	67.91±5.82	0.229
40 MIN	64.23±6.12	65.42±5.91	0.388
50 MIN	63.33±4.21	63.81±5.76	0.676
60 MIN	62.19±6.33	66.42±5.99	0.003
POST OP	72.7±6.16	74.63±6.88	0.198

NS-not significant, HS-highly significant, S-significant

Total duration of pneumoperitoneum in dexmedetomidine group was 52.76±12.67 minutes and in propofol group was 57.36±15.34 minutes with p value of 0.155 [Table11]. The time to extubation was 16.80±4.26 minutes in dexmedetomidine group and 14.98±5.42 minutes in propofol group and was statistically insignificant with p-value of >0.05 [Table11]. Two patients in group dexmedetomidine had fall in systolic blood pressure >30% of baseline value and was treated with single dose of injection ephedrine 6 mg while in propofol group the same happened in one patient and was accordingly treated. No incidence of bradycardia requiring pharmacological intervention was noted in any group. Four patients in group propofol required bolus rescue dose of fentanyl 30 µg in the intra operative period. Only one patient needed rescue dose of fentanyl in the dexmedetomidine group.

Table 11: Comparison of other variables between two groups

Criteria	Group D n=39	Group P n=38	P value
Duration of pneumoperitoneum(min)	52.76±12.67	57.36±15.34	0.155 (NS)
Time to extubation(min)	16.80±4.26	14.98±5.42	0.105 (NS)
Hypotension	2	1	NS
Rescue fentanyl	1	4	S

NS-not significant, HS-highly significant, S-significant

DISCUSSION

For surgical procedures done under general anesthesia, intraoperative control of hemodynamic parameters and smooth and early extubation is of paramount importance in improving overall patient outcome. Creation of pneumoperitoneum during laparoscopic surgery cause sympathetic nervous stimulation due to stretching of abdominal wall, resulting in a hemodynamic response associated with increase in blood pressure and tachycardia.[3] This increase in heart rate and blood pressure may be deleterious in certain patient populations like elderly, ischemic heart disease, etc. Adequate control of this sympathetic response to pneumoperitoneum creation is a challenging situation for the

anaesthesiologist. This study was designed to study effect of dexmedetomidine infusion in a dose of 0.2 to 0.7 $\mu g.kg^{-1}.h^{-1}$ without loading dose in attenuation of hemodynamic stress response to pneumoperitoneum creation in comparison to propofol infusion (25-75 $\mu g.kg^{-1}.min^{-1}$). The results of this study suggest that dexmedetomidine infusion is effective in attenuating the hemodynamic response to pneumoperitoneum in patients undergoing laparoscopic cholecystectomy and may be a better alternative to propofol in attenuating such response. Dexmedetomidine is a highly selective α_{-2} agonist with central sympatholytic activity. It exerts its sympatholytic effect by activating α_{-2} receptors in medullary vasomotor centre. Activation of these receptors results in decreased central sympathetic outflow. As hemodynamic response to pneumoperitoneum creation is because of sympathetic stimulation, dexmedetomidine seems to be appropriate drug for suppression of this response. Dexmedetomidine has been shown to cause a decrease in serum norepinephrine concentration. It also stimulates parasympathetic outflow as a result of activation of receptors in locus ceruleus of brainstem.[10,11,12,] Main side effects with dexmedetomidine use are bradycardia and hypotension. These side effects are more common with loading dose. As loading dose of dexmedetomidine was omitted in our study, no incidence of bradycardia or hypotension requiring intervention was noted in our study with dexmedetomidine use. The results of our study are similar to a study conducted by Bhutia MP *et al.*[13] who compared dexmedetomidine (maintenance dose only) and propofol infusions for attenuation of hemodynamic response to pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. They observed that during the intraoperative period dexmedetomidine was comparable to propofol. However on extubation, hemodynamic parameters were better controlled with dexmedetomidine. They conclude that dexmedetomidine infusion in a loading dose of 0.2-0.7 mcg/kg/hr provides stable hemodynamics without any side effects in patients undergoing laparoscopic cholecystectomy. Our study findings are in concordance with a study conducted by Shah V *et al.* They compared dexmedetomidine and propofol for haemodynamic changes and depth of anaesthesia (using BIS monitor) during laparoscopic surgery.[14] They found dexmedetomidine to be superior to propofol for hemodynamic control of pressor response to pneumoperitoneum. However, in their study dexmedetomidine was used in both loading and maintenance dose. Also BIS monitoring was not done in our study. The results of our study are also in correlation with a study conducted by Manne GR *et al.*,[15] who used dexmedetomidine in doses of 0.2 µg/kg/hr and 0.4 µg/kg/hr to assess its effect on haemodynamic stress response, sedation and postoperative analgesic requirement in patients undergoing laparoscopic surgeries and concluded that low dose dexmedetomidine infusion in the dose of 0.4 mcg/kg/h effectively attenuates haemodynamic stress response during laparoscopic surgery with reduction in post-operative analgesic requirements. Bhattacharjee *et al.* also observed that dexmedetomidine reduces the elevation of mean arterial pressure and heart rate during and after pneumoperitoneum and thereby improving perioperative haemodynamic stability during laparoscopic surgery There was no significant prolongation of time to extubation by dexmedetomidine use in our study. Bhattacharjee *et al.*[16] also observed no significant effect of dexmedetomidine on response to verbal command and extubation time. In the study by Bhutia MP *et al*[13] there was also no prolongation of time to extubation by dexmedetomidine when compared to propofol.

LIMITATIONS

Our study could not be blinded as the doses of dexmedetomidine and propofol are different and knowledge of the drug administered is required for adjustments of drug dosage.

CONCLUSION

Dexmedetomidine infusion without loading dose is effective in attenuating hemodynamic response to pneumoperitoneum in patients undergoing laparoscopic cholecystectomy and is better alternative to propofol in such patients.

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