A Prospective Randomized Double Blind Controlled Study Evaluating the Effects of Dexmedetomidine on Haemodynamic Status in Patients Undergoing Laparoscopic Assisted Vaginal Hysterectomy

Ashwini G S[1], Kamala G R[2], Ramesh.K[3]

[1,2]Assistant Professor, Department of Anesthesia, Basaveshwara Medical College Hospital and Research Centre, Chitradurga, Karnataka
[3]Associate Professor, Department of Community Medicine, VIMS, Ballari, Karnataka

Corresponding Author:
E-mail: ramspsm@gmail.com

ABSTRACT

Background: *Intraoperative hypertension and tachycardia are common hemodynamic disturbances in patients undergoing laparoscopic assisted vaginal hysterectomy. In addition there is increase in systemic vascular resistance, and is associated with a decrease in cardiac index and metabolic changes. Dexmedetomidine a centrally acting α-2 agonist has been particularly effective in blunting the haemodynamic response to tracheal intubation and pneumoperitoneum.*

Methodology: *Sixty patients, scheduled for elective laparoscopic assisted vaginal hysterectomy belonging to ASA class I and II, in the age group 38 to 55 years were included in the study and they were assigned randomly into two groups.Group D (n=30): received dexmedetomidine as a bolus of 0.6 µg/kg body weight (0.3 ml/kg body weight) over 10 min intravenously, 10 min before induction, followed by infusion at a rate of 0.2 µg/kg/hr(0.1 ml/kg/hr) throughout the surgery. Group C (n=30): received bolus of normal saline at a rate of 0.3 ml/kg body weight in 50 ml syringe over 10 min intravenously, 10 min before induction followed by infusion at a rate of 0.1 ml/kg/hrthroughout the surgery.*

Results: *It was noted that HR, SBP, DBP and MAP in group D were significantly decreased after intubation, throughout the period of pneumoperitoneum and after extubation. In addition dexmedetomidine produced arousable sedation after extubation, decreased the incidence of post operative nausea and vomiting without significant side effects like bradycardia and hypotension.*

Conclusion: *Dexmedetomidine as a single bolus dose of 0.6 µg/kg body weight and continuous infusion at a rate of 0.2 µg/kg/hr was seen to effectively attenuate the haemodynamic response to laryngoscopy and tracheal intubation and also to pneumoperitoneum without any side effects.*

Keywords: *Dexmedetomidine; Haemodynamic response; Laparoscopic assisted vaginal hysterectomy.*

Access this article online	
Quick Response Code:	**Website:** www.innovativepublication.com
	DOI: 10.5958/2394-4994.2015.00035.9

INTRODUCTION

Laparoscopic assisted vaginal hysterectomy (LAVH) is becoming more popular these days and abdominal and vaginal hysterectomies are nowadays challenged by laparoscopic hysterectomy[1]. The relation between hemodynamic depression and the level of intra-abdominal pressure is influenced by CO_2-absorption, spontaneous respiration, and mechanical ventilation, changes in intravascular volume, the surgical trauma and general anaesthesia.[2]

Laparoscopic surgeries require creation of pneumoperitoneum (PNP) which is produced by insufflations of Carbon Dioxide (CO_2) in the abdominal cavity by using automated flow controlled CO_2 Insufflator which supplies gas till the required intra-abdominal pressure is reached[3]. After creation of PNP, intra-abdominal pressure increases along with the increase in circulating blood volume which is due to shifting of blood from the splanchnic capacitance blood vessels. Initially moderate increase in intra-abdominal pressure raises cardiac output and mean arterial pressure.[4]Asintra-abdominal pressure further raises circulating blood volume falls as venous return decreases and there is a fall in cardiac output.

This fall in cardiac output is troublesome in hypovolemic patients and patients receiving anesthetic agents with cardiac depressant effects.Laparoscopy induces significant hemodynamic changes and leads to increased Systemic Vascular Resistance (SVR) and Pulmonary Vascular Resistance (PVR), increases in Mean Arterial Pressure (MAP), reduction in Stroke Volume (SV), Cardiac Output (CO), and the mechanism is mechanical and humoral mediated.[5]

Numerous agents and combination of agents have been used in an effort to minimize the hemodynamic instability during this period. Volatile agents like isoflurane[5] and sevoflurane[6] along with opioids[7] have traditionally been used for blunting the perioperative stress response during general anesthesia. There has been limited success in maintaining hemodynamic stability as volatile agents decrease

surgical stimulus induced catecholamine secretion but not the cortisol secretion.[6] Clonidine is known to induce sedation, decrease anaesthetic drug requirement and improve perioperative haemody-namics by attenuating blood pressure and heart rate responses to surgical stimulation, and protection against perioperative myocardial ischaemia. It provides sympathoadrenal stability and suppresses renin angiotensin activity. There are studies indicating benefits of using clonidine for maintenance of haemodynamic stability in laparoscopic surgeries.[8,9,10]

Dexmedetomidine is considered full agonist at α-2 receptors as compared to clonidine which is considered as a partial agonist. Similar to clonidine, dexmedetomidine also attenuates the hemodynamic response to tracheal intubation, decreases plasma catecholamine concentration during anesthesia and decreases perioperative requirements of inhaled anaesthetics.[12] As LAVH is routinely performed surgery these days, it is desirable to have a stable intraoperative hemodynamic status. Hence in this study, it has been attempted to study the effect of the α-2 agonist dexmedetomidine in maintaining the Hemodynamic status.

METHODOLOGY

The present study was conducted in the Department of Anesthesiology, at a tertiary care hospitalfor a period of one year. The study was undertaken after obtaining ethical committee clearance as well as informed consent from all patients.Sixty patients, scheduled for elective LAVH belonging to ASA class I and II were included in the study.

Randomization:

Based on the computer generated randomization numbers, patients were randomly divided into two groups with 30 patients in each group.

Group C (Control group; n=30) - Received normal saline as bolus and infusion

Group D (Dexmedetomidine group; n=30) - Received intravenous dexmedetomidine as single bolus dose of 0.6 μg/kg body weight and continuous infusion at a rate of 0.2 μg/kg/hr.

Patients fulfilling selection criteria were selected for the study and briefed about the nature of study and explained about anesthetic procedure. A thorough pre-anesthetic evaluation was done on the evening before surgery. The study drug was provided as prefilled identical 50 ml syringes containing study drugs, as per the randomization protocol, in dilutions of:

1. Normal saline 0.9% - 50 ml
2. Dexmedetomidine 50 ml (2 μg/ml)

All patients included in the study were premeditated with tablet alprazolam 0.5 mg and tablet ranitidine 150 mg orally at bed time the previous night before surgery. They were kept nil orally 10 pm onwards on the previous night.The investigators involved in the study did not know about the content of the syringes as the preparation of the study drug was done by an anesthesiologist not involved with the observations made for the study. Patients were explained about the study, but did not know which drug was used. On arrival of the patient in the operating room, two IV lines were secured, one 20 G IV cannula in right hand for the infusion and another 18 G IV cannula in left hand for intravenous fluids and drug administration. 500 ml of crystalloids (Ringer Lactate) was started. HR, SBP, DBP and MAP were monitored before, during and after the surgery. End tidal carbon dioxide was monitored intraoperatively and kept between 30 to 35 mm Hg.

Study drug dexmedetomidine was prepared with 100 μg diluted in 50 ml of normal saline with each ml containing 2 μg. Group D patients were given dexmedetomidine as a bolus of 0.6 μg/kg body weight (0.3 ml/kg body weight) over 10 min intravenously, 10 minbefore induction, followed by infusion at a rate of 0.2 μg/kg/hr (0.1 ml/kg/hr) throughout the surgery. Group C patients served as control were given bolus of normal saline at a rate of 0.3 ml/kg body weight in 50 ml syringe over 10 min intravenously, 10 min before induction followed by infusion at a rate of 0.1 ml/kg/hrthroughout the surgery.

Patients in both the groups were induced with Inj. Fentanyl 1μg/kg, Inj. Propofol2 mg/kg, Inj. Rocuronium 0.9 mg/kg and preservative free Inj. Lidocaine 1 mg/kg. Laryngoscopy and endotracheal intubation were done 90 seconds after administration of InjLidocaine. Anaesthesia was maintained with O_2 in N_2O (66%:33%), isoflurane 1% and intermittent bolus dose of rocuronium. The data was entered in Microsoft excel and was analyzed in SPSS. The statistical tests used were proportion, Mean, standard deviation and Independent T test

RESULTS

The analysis was mainly based on setting an alpha error at 5% and beta error at 20% keeping the power of the study to 80%. Hence the p value which is less than 0.05, is considered to be significant. Average age in group C (Control) was 45.10 years and in group D (Dexmedetomidine) was 44.87 years. Both groups were similar with respect to age (p=0.844). Average weight in group C was 64.77 kg and in group D was 66.93 kg. There was no significant difference in body weight of patients between group C and group D (p=0.298). Average duration of surgery in both group C and group D was 100 min.

Table 1: Showing the intergroup comparison of mean heart rate (HR/min) changes in response to laryngoscopy and intubation and pneumoperitoneum (PNP) between control group and dexmedetomidine group

Time interval	Group C	Group D	'p' value
Basal (M1)	77.53±10.91	80.53±7.78	0.225(NS)
After bolus drug (M2)	76.40±10.36	66.10±6.34	0.000(HS)
After induction (M3)	75.73±10.48	64.83±5.72	0.000(HS)
1 min after intubation (M4)	105.70±11.93	65.87±4.57	0.000(HS)
3 min after intubation (M5)	93.07±10.48	68.93±6.01	0.000(HS)
5 min after intubation (M6)	76.50±11.73	65.20±4.37	0.000(HS)
Before PNP (M7)	74.27±12.57	63.00±5.02	0.000(HS)
10 min after PNP (M8)	85.70±17.12	66.87±5.26	0.000(HS)
20 min after PNP (M9)	83.47±12.66	58.27±4.84	0.000(HS)
30 min after PNP (M10)	82.60±13.39	58.33±5.46	0.000(HS)
After abdomen deflation (M11)	74.33±9.95	58.47±5.58	0.000(HS)
Vaginal part (M12)	73.10±9.50	59.17±6.28	0.000(HS)
After extubation (N1)	80.17±12.28	59.70±4.25	0.000(HS)
Post operative (N2)	72.47±8.39	80.47±6.66	0.000(HS)

Highly significant (HS); Significant (S); Not significant (NS)

Mean HR in group C (Control) increased significantly at 1 (M4) and 3 (M5) min after intubation, 10 (M8), 20 (M9) and 30 (M10) min after pneumoperitoneum (M10) and after extubation (N1) when compared to basal value and group D (Dexmedetomidine) which is statistically highly significant (p=0.000) whereas in group D (Dexmedetomidine) there was a significant fall in mean HR at 1 (M4), 3 (M5) and 5 (M6) min after intubation, 10 (M8), 20 (M9) and 30 (M10) min after pneumoperitoneum (M10) and after extubation (N1) compared to basal value and group C (Control) (p=0.000).

Table 2: Showing the intergroup comparison of mean systolic blood pressure (SBP in mm Hg) changes in response to laryngoscopy and intubation and pneumoperitoneum (PNP) between control group and dexmedetomidine group.

Time Interval	Group C	Group D	'p' value
Basal (M1)	123.97±11.44	126.53±9.06	0.339(NS)
After bolus drug (M2)	125.40±10.97	108.07±10.13	0.000(HS)
After induction (M3)	113.90±14.14	107.03±9.95	0.034(NS)
1 min after intubation (M4)	147.77±13.01	116.03±6.40	0.000(HS)
3 min after intubation (M5)	131.60±11.36	111.03±5.67	0.000(HS)
5 min after intubation (M6)	120.47±12.04	106.30±5.22	0.000(HS)
Before PNP (M7)	115.10±11.35	104.47±6.04	0.000(HS)
10 min after PNP (M8)	148.63±11.81	110.33±6.84	0.000(HS)
20 min after PNP (M9)	136.70±10.90	99.57±5.79	0.000(HS)
30 min after PNP (M10)	134.20±10.49	100.73±6.02	0.000(HS)
After abdomen deflation (M11)	124.80±8.12	100.53±5.75	0.000(HS)
Vaginal part (M12)	121.30±6.00	102.63±7.75	0.000(HS)
After extubation (N1)	132.67±6.81	101.33±6.40	0.000(HS)
Post operative (N2)	122.27±8.33	126.17±8.41	0.076(S)

Highly significant (HS); Significant (S); Not significant (NS)

Mean SBP in group C (Control) increased significantly at 1 (M4) and 3 (M5) min after intubation, 10 (M8), 20 (M9) and 30 (M10) min after pneumoperitoneum (M10) and after extubation (N1) when compared to basal value and group D (Dexmedetomidine) which is statistically highly significant (p=0.000) whereas in group D (Dexmedetomidine) there was a significant fall in mean SBP at 1 (M4), 3 (M5) and 5 (M6) min after intubation, 10 (M8), 20 (M9) and 30 (M10) min after pneumoperitoneum (M10) and after extubation (N1) compared to basal value and group C (Control) (p=0.000).

Table 3: Showing the intergroup comparison of mean diastolic blood pressure (DBP in mm Hg) changes in response to laryngoscopy and intubation and pneumoperitoneum (PNP) between control group and dexmedetomidine group

Time Interval	Group C	Group D	'p' value
Basal (M1)	77.40±8.79	80.03±6.36	0.339(NS)
After bolus drug (M2)	77.83±8.23	68.83±8.51	0.000(HS)
After induction (M3)	71.73±8.33	68.63±7.73	0.034(HS)
1 min after intubation (M4)	91.60±6.54	75.03±6.54	0.000(HS)
3 min after intubation (M5)	83.67±8.83	70.77±7.71	0.000(HS)
5 min after intubation (M6)	77.27±10.55	66.20±6.46	0.000(HS)
Before PNP (M7)	73.07±9.44	65.70±6.97	0.000(HS)
10 min after PNP (M8)	94.97±8.50	70.67±7.13	0.000(HS)
20 min after PNP (M9)	88.93±7.37	60.87±8.12	0.000(HS)
30 min after PNP (M10)	87.67±7.12	63.00±8.80	0.000(HS)
After abdomen deflation (M11)	80.03±8.03	61.70±5.92	0.000(HS)
Vaginal part (M12)	76.33±7.38	63.13±6.61	0.000(HS)
After extubation (N1)	83.70±7.77	63.13±8.63	0.000(HS)
Post operative (N2)	76.30±6.95	80.53±6.18	0.016(HS)

Highly significant (HS); Significant (S); Not significant (NS)

Mean DBP in group C (Control) increased significantly at 1 (M4) and 3 (M5) min after intubation, 10 (M8), 20 (M9) and 30 (M10) min after pneumoperitoneum (M10) and after extubation (N1) when compared to basal value and group D (Dexmedetomidine) which is statistically highly significant (p=0.000) whereas in group D (Dexmedetomidine) there was a significant fall in mean DBP at 1 (M4), 3 (M5) and 5 (M6) min after intubation, 10 (M8), 20 (M9) and 30 (M10) min after pneumoperitoneum (M10) and after extubation (N1) compared to basal value and group C (Control) (p=0.000).

Table 4: Showing the intergroup comparison of mean arterial blood pressure (MAP in mm Hg) changes in response to laryngoscopy and intubation and pneumoperitoneum (PNP) between control group and dexmedetomidine group.

Time Interval	Group C	Group D	'p' value
Basal (M1)	92.97±9.43	95.50±6.70	0.107(NS)
After bolus drug (M2)	93.97±8.71	82.00±7.94	0.000(HS)
After induction (M3)	85.73±9.76	81.43±7.58	0.034(HS)
1 min after intubation (M4)	110.33±9.07	88.67±5.71	0.000(HS)
3 min after intubation (M5)	99.67±9.06	84.23±6.73	0.000(HS)
5 min after intubation (M6)	91.67±10.52	79.50±5.43	0.000(HS)
Before PNP (M7)	87.10±9.47	78.60±5.98	0.000(HS)
10 min after PNP (M8)	112.87±8.99	83.83±6.59	0.000(HS)
20 min after PNP (M9)	104.80±7.95	73.53±6.13	0.000(HS)

30 min after PNP (M10)	103.17±7.68	74.87±5.96	0.000(HS)
After abdomen deflation (M11)	94.90±7.56	74.87±5.07	0.000(HS)
Vaginal part (M12)	91.43±6.18	76.23±6.33	0.000(HS)
After extubation (N1)	100.10±6.57	76.13±7.36	0.000(HS)
Post operative (N2)	91.53±6.93	95.70±6.20	0.0017(HS)

Highly significant (HS); Significant (S); Not significant (NS)

Mean MAP in group C (Control) increased significantly at 1 (M4) and 3 (M5) min after intubation, 10 (M8), 20 (M9) and 30 (M10) min after pneumoperitoneum (M10) and after extubation (N1) when compared to basal value and group D (Dexmedetomidine) which is statistically highly significant (p=0.000) whereas in group D (Dexmedetomidine) there was a significant fall in mean MAP at 1 (M4), 3 (M5) and 5 (M6) min after intubation, 10 (M8), 20 (M9) and 30 (M10) min after pneumoperitoneum (M10) and after extubation (N1) compared to basal value and group C (Control) (p=0.000).

DISCUSSION

Changes in heart rate (HR)

Table 5: Showing mean HR changes in various studies following dexmedetomidine administration

Sl. No.	Author and year	Dose (per kg body weight)	Mean change in HR (bpm) 10 min after dexmedetomidine administration
1.	Aho et al.[13]- 1991	0.6µg	+4
2.	Aho et al.[14] -1991	0.4µg	-
3.	Scheinin et al.[15]-1992	0.6µg	-10
4.	Jaakola et al.[16]-1992	0.6µg	-5
5.	Basar et al.[17]-2008	1µg	-9
6.	Kunisawa et al.[18] – 2009	1µg	-14
7.	Keniya et al.[19] – 2011	1µg	-10
8.	**Present study**	**0.6µg**	**-14**

The sign (-) denotes decrease and (+) denotes increase in HR. The spaces which have been left blank ('–'), are the parameters not studied by the authors.

As per above table, various authors[20,21] have found that dexmedetomidine decreased the HR between 5 bpm to 14 bpm 10 min after bolus administration. Our study also found similar change in HR which is statistically highly significant. In the dexmedetomidine group there was a decrease of 14 bpm in mean HR compared to control group where there was a decrease of 1 bpm which is statistically highly significant (p=0.000).

Changes in systolic blood pressure (SBP)

Basal mean SBP were comparable in both control and dexmedetomidine groups.

After bolus drug administration (M2)

Compared to the basal value, in the dexmedetomidine group there was a decrease of 18.46 mm Hg in SBP which is statistically significant (p=0.000).Similar observation was made by Ahoet al.[13] and Keniya et al.[22]wherein they found a significant fall in mean SBP 10 min after drug administration.In the control group there was a negligible increase of 1.43 mm Hg compared to basal which is not statistically significant (p=0.232).

After induction (M3)

Compared to the basal values, in the control group there was a decrease of 10 mm Hg of SBP whereas in dexmedetomidine group there was a decrease of 20 mm Hg which is statistically highly significant. Similar observations were made by Kunisawaet al.[18] where in there was decrease in SBP by 12 mm Hg in dexmedetomidine group which concurs with our study. Compared to preinduction values there was a fall of just 1 mm Hg in dexmedetomidine group and 11.5 mm Hg in control group.

Table 6: Showing changes in SBP after tracheal intubation at various intervals in control and dexmedetomidine group

Sl. No.	Author and year	Mean change in SBP (mm Hg) following intubation in control group			Mean change in SBP (mm Hg) following intubation in dexmedetomidine group		
		1 min	3 min	5 min	1 min	3 min	5 min
1.	Aho et al.[13]-1991	+48	-	-	+48	-	-
2.	Schenin et al.[15]-1992	-	-	-18	-	-	-22
3.	Jaakola et al.[16]-1992	-	-	+	-	-	-17
4.	Kunisawa et al.[18]-2009	+10	-	-	-15	-	-
5.	Keniya et al.[19] - 2011	+30	-	+10	-10	-	-20
6.	**Present study**	**+23.8**	**+7.63**	**-3.5**	**-10.5**	**-15.5**	**-20.23**

The sign (-) denotes decrease and (+) denotes increase in SBP. The spaces which have been left blank ('–'), are the parameters not studied by the authors.

From above table, it is seen that dexmedetomidine blunts the increase in systolic blood pressure at 1, 3 and 5 min following laryngoscopy and intubation compared to control group (p=0.000) which is statistically highly significant.

At 1st, 3rd and 5th min (M4, 5, 6)

In our study, following laryngoscopy and intubation at 1st and 3rd min, the mean SBP increased by 23.8 and 7.63 mm Hg respectively in the control group whereas in dexmedetomidine group the mean SBP decreased by 10.5 and 15.5 mm Hg respectively which is statistically highly significant (p=0.000).

Aho et al.[13] noted a increase in SBP by 48 mm Hg and 18 mm Hg in control group and dexmedetomidine group respectively at 1 min after intubation which was statistically significant.

In dexmedetomidine group, at the 1st min, there is an increase of 9 mm Hg of SBP compared to the values immediately after induction, but compared to the basal value the reduction in SBP is 10.5 mm Hg. Even at 5th min the SBP did not reach the basal value and it was 20 mm Hg lower than the basal value. In the control group, the increase in SBP was maximum at 1st min but reached the basal value by 5th min. This is probably due to the use of lignocaine before laryngoscopy and intubation in our study which was not used in above mentioned studies.

Scheinin et al.[15] observed increase in SBP by 18 mm Hg immediately after intubation compared to the values after induction, but the SBP was less than the basal values. This compares with our study. They also observed an increase in SBP by 25 mm Hg in control group compared to basal value.

Jaakola et al.[16] have observed a fall of 17 mm Hg in SBP 5 min after intubation in dexmedetomidine group and in control group an increase of SBP by 10 mm Hg, compared to the basal values.

Changes in diastolic blood pressure (DBP)

Basal mean DBP were comparable in both control and dexmedetomidine groups.

After bolus drug administration (M2)

Compared to the basal value, in the dexmedetomidine group there was a decrease of 11 mm Hg in mean DBP which is statistically significant (p=0.000). In the control group the DBP was same as compared to basal which is not statistically significant (p=0.651).Similar observations were found by Kunisawaet al.[18] and Keniya et al.[19] where there was a decrease in DBP in dexmedetomidine group and no change in control group.

Ahoet al.[13] observed a continuous decrease of DBP in dexmedetomidine group till induction which concurs with our study.

After induction (M3)

Compared to basal value, in the control group there was a reduction of 6 mm Hg of DBP and 11 mm Hg in dexmedetomidine group. Jaakola et al.[16] found a decrease in DBP by 3 mm Hg in control group and 15 mm Hg in dexmedetomidine group which compares with the present study.

Compared to preinduction values there was a fall of 6 mm Hg in control group, whereas no change in dexmedetomidine group.

After laryngoscopy and intubation

Table 6: Showing comparison of mean DBP changes in control and dexmedetomidine group following intubation at various intervals

	Mean changes in DBP (mm Hg) following intubation		
	1 min	**3 min**	**5 min**
Control	+14.2	+6.27	Same as basal
Dexmedetomidine	-5	-9.26	-13.83
'p' value	0.000	0.000	0.000

The sign (-) denotes decrease and (+) denotes increase in DBP.

Changes in mean arterial pressure (MAP)

At 1st min, in dexmedetomidine group, there is an increase of MAP by 7 mm Hg compared to the values immediately after induction, but compared to the basal values there is a reduction in MAP by 6 mm Hg. Even at 5th min the MAP was lower by 16 mm Hg, compared to the basal values in dexmedetomidine group which is statistically highly significant.

However, in control group there is an increase in MAP by 24 mm Hg compared with 7 mm Hg of increase in dexmedetomidine group in comparison with the values of MAP immediately after induction which is statistically significant.At 1st min after intubation, the increase in MAP in control group was 17 mm Hg whereas in dexmedetomidine group there was a fall in MAP by 6 mm Hg which is statistically highly significant.

Mowafi et al.[23] observed an increase in MAP by 5 mm Hg immediately after intubation in dexmedetomidine group compared to an increase of 12 mm Hg in control group in comparison with values after induction. Basaret al.[21] noted a decrease in MAP by 10 mm Hg in dexmedetomidine group at 5th min which compares with our study.

CONCLUSION

Dexmedetomidine as a single bolus dose of 0.6 µg/kg body weight and continuous infusion at a rate of 0.2 µg/kg/hr significantly obtunded the haemodynamic response to laryngoscopy and tracheal intubation and also to pneumoperitoneum in patients undergoing laparoscopic assisted vaginal hysterectomy without significantly prolonging the recovery time. In addition dexmedetomidine produced arousable sedation after extubation, decreased the incidence of post operative nausea and vomiting without significant side effects like bradycardia and hypotension.

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