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Efficacy of intravenous ketamine as premedicant for prevention of intraoperative hypotension after spinal anesthesia in parturients posted for elective cesarean section

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ABSTRACT

Background: Hypotension following spinal anesthesia (SA) in lower segment cesarean section can be deleterious to the parturient and to fetus. Ketamine acts by stimulating the cardiovascular system leading to high blood pressure and increase in heart rate (HR) and cardiac output. **Aims and Objectives:** This study aimed to assess the efficacy of 15 mg of prophylactic intravenous ketamine in elective cesarean section for prevention of hypotension after SA. **Materials and Methods:** This double-blinded randomized controlled study was conducted on 98 participating parturients who were American Society of Anesthesiologists term pregnant women. The parturients were randomly divided into two groups (n = 49 in each). All the parturients received SA. Ketamine group - Group K received 15 mg of ketamine IV bolus in 3 mL saline and control group - Group C received the same volume of normal saline IV bolus. HR and systolic blood pressure (SBP) were recorded at baseline at 5, 10, 15, and 20 min after the injection and then every 15 min till the end of the operation. Incidences of hypotension were recorded. The total number dose of ephedrine used, APGAR score, and Visual Analog Scale scores were recorded. The Ramsay Sedation Score was also recorded at baseline, then 5, 10, 15, 30, and 45 min after injection, and then at the end of the operation. **Results:** This study showed a statistically significant increase in the incidence of hypotension and higher use of intravenous ephedrine 6 mg boluses in the control group when compared to the ketamine group. Forty-two parturients in the control group developed hypotension compared to 23 parturients in the ketamine group with $P < 0.001$. The total ephedrine dose was significantly lower among the ketamine group. Sedation was observed for the first 15 min intraoperatively in the ketamine group with $P = 0.001$. There was no statistically significant difference in APGAR score between the two groups. **Conclusion:** There was significantly higher hemodynamic stability in the ketamine group with regard to SBP, diastolic blood pressure, and HR. Hence, low-dose ketamine, when used as a premedicant, is an effective agent that can be used in preventing post-spinal intraoperative hypotension in parturients undergoing cesarean section delivery.

Key words: Cesarean section delivery; Ketamine; Neonatal response; Post-spinal hypotension; Spinal anesthesia

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INTRODUCTION

Anesthesia to a parturient is unique and requires the highest degree of care because the anesthesiologist has to cater to two individuals - the mother and the fetus. Cesarean section is one of the most commonly performed surgical procedures.[1] Spinal anesthesia (SA) has been the anesthetic technique of choice for cesarean section as it has many

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advantages over general anesthesia (GA).[2] In SA airway, manipulation can be avoided as parturients are considered to have difficult airway and full stomach. Parturients can remain fully awake, thus facilitating earlier bonding and breastfeeding with the baby. SA also provides excellent postoperative analgesia.

SA causes sympathetic blockade and decreased venous return. Systolic hypotension more than 20–30% of parturient's baseline blood pressure is of particular importance. It can lead to maternal low perfusion pressure and uteroplacental hypoperfusion and may lead to nausea-vomiting, dizziness, and low consciousness, leading to fetal bradycardia and acid–base abnormalities which may lead to neurobehavioral changes later. Fetal acidosis may result in weak rooting and suckling reflexes of infants that can severely compromise the establishment of breastfeeding post-delivery.[3,4]

Degree of hypotension after SA depends upon their baseline peripheral vasomotor tone, their volume status, and their sympathetic activity as hypotension occurs due to decrease in the systemic vascular resistance due to blockade of preganglionic sympathetic fibers.[5] This sympathetic block causes the reduction in cardiac output (CO) and mean arterial pressure (MAP) and thus the decrease in perfusion to placenta and to vital organs.

Pregnant women are more likely to develop hypotension following SA due to their decreased peripheral vascular tone, especially at term. Furthermore, multiparous women have increased sensitivity to local anesthetics and less responsiveness to vasopressors.[6] Therefore, parturients with low baseline peripheral vasomotor tone will be at high risk of developing post-SA hypotension. Hence, it is important to treat it preoperatively.

Ketamine is a phencyclidine derivative. It is a non-competitive antagonist at the N-methyl-D-aspartate and acts by stimulating the cardiovascular system leading to prevent fall of blood pressure and increase in heart rate (HR) and CO. Direct stimulation of the central nervous system (CNS) leading to increased sympathetic nervous system outflow seems to be the most important mechanism for cardiovascular stimulation.[7]

Aims and objectives

This study aimed to assess the efficacy of 15 mg of prophylactic intravenous ketamine in elective cesarean section for prevention of hypotension after spinal anesthesia.

MATERIALS AND METHODS

This double-blinded randomized controlled study was conducted in a tertiary hospital after approval of the research ethical committee (clinical trials ID is CTRI/2022/08/044629) and obtaining written informed consent from all the participants. It included 98 patients admitted for elective cesarean section; all were term pregnant and of American Society of Anesthesiologists physical status grade II. Parturients who had pre-eclampsia, chronic hypertension, cardiovascular troubles, any contraindication to regional anesthesia such as local infection or bleeding disorders, or any hypersensitivity to ketamine were excluded from the study.

All the parturients were randomly allocated into two groups using a computer-generated random number list and opaque sealed envelopes. The study drugs were prepared by the same anesthesiologist who did the randomization and administered by the observer. Hence, the observer and parturient were blinded to the study drugs.

Parturients were divided into two groups:

- Ketamine group received 15 mg of intravenous ketamine in 3 ml of normal saline
- Control group received 3 ml of normal saline.

Each parturient was prehydrated with 500 mL of Ringer's lactate (RL) over 20 min prior to the subarachnoid block. Standard anesthesia monitoring was applied. SA was performed using Quincke's 25-gauge spinal needle in lateral position with 10 mg of injection bupivacaine 0.5% (hyperbaric) at the L3-L4 interspace with midline approach. After administration of spinal anesthesia, the parturients were placed in supine position.

Left lateral displacement of uterine was given by keeping wedge below right hip.

Ringer lactate was given to prevent spinal anesthesia induced hypotension.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), HR, respiratory rate, and SpO_2 were recorded at 2-min intervals after the SA up to 20 min and then at 5-min intervals till the end of surgery.

Hypotension was defined as decrease in SBP >20% of baseline or <90 mmHg and was treated with IV bolus of 6 mg of injection ephedrine. The number of incidences of hypotension, total amount of ephedrine required, and number of doses of ephedrine required were recorded. The first 60 min following SA was considered for anesthesia-induced hypotension. The incidence of nausea, vomiting, and mood changes (hallucinations) was recorded intraoperatively and till 2 h postoperatively. APGAR scores of neonates were measured at the 1st and 5th min after childbirth.

Post-operative observation and monitoring of SBP, DBP, HR, electrocardiogram, and SPO_2 was done for 2 h. Post-operative pain was assessed using the Visual Analog Scale (VAS). The pain was monitored every 2 h for the first 6 h and then every 6th hourly for the next 18 h or until the first complaint of pain called the "time to first breakthrough pain" which was considered the pain requiring treatment (VAS ≥4). Rescue analgesic injection diclofenac 75 mg was given intramuscularly. The number of doses given was recorded.

Sedative effects at baseline, then at 5, 10, 15, 30, and 45 min after the intrathecal injection, and then at the end of the operation were recorded using the Ramsay Sedation Scale.

Statistical methods

Sample size

Assuming an estimated difference in incidence of hypotension between the ketamine and control groups as 20%,[1,8] with a power of 80% and an alpha error of 5%, sample size of 49 subjects in each group needed to be studied. A total of 98 parturients were considered, out of which 49 parturients received 15 mg of ketamine and the rest 49 parturients received normal saline.

Data were entered into Microsoft Excel data sheet and were analyzed using SPSS 22 version software. Categorical data were represented in the form of frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data were represented as mean and standard deviation. Independent t-test or Mann-Whitney U test was used as test of significance to identify the mean difference between two quantitative variables and qualitative variables, respectively.

Independent t-test was used to compare age, weight, height, body mass index (BMI), and APGAR score between the two groups. Graphical representation of data: MS Excel and MS Word were used to obtain various types of graphs such as bar diagram and line diagram. P-value (probability that the result is true) of <0.05 was considered statistically significant after assuming all the rules of statistical tests.

Statistical software

MS Excel and SPSS version 22 (IBM SPSS Statistics, Somers, NY, USA) were used to analyze data.

RESULTS

The demographic profile (mean age, mean height, mean weight, and mean BMI) and baseline HR were similar in both the groups.

In group C the incidence of hypotension was 85.71% which is significant (42 of 49 parturients in group C had hypotension). Whereas, in Group K, 46.93% (23 out of 49 parturients) had hypotension (P=0.001) (Table 1).

A significantly higher mean HR was observed in Group C from the 1st min (0.037) which continued till 15 min (P=0.005). Again, significantly higher mean HR was observed in Group C at 19, 25, 35, and 40 min as compared to Group K, which explains the compensatory rise in the HR due to higher incidence of hypotension in Group C (Table 2).

A significantly higher fall in SBP was observed in Group C by the 1st min (P=0.029) which continued till the 13th min (P=0.002) as compared to Group K. There was a statistically significantly higher SBP from the 40th min to the 60th min in Group C as compared to Group K which correlated with the administration of ephedrine (Table 3).

A statistically significant difference was observed in mean DBP of the two groups at the 1st min till the 13th min, with values being lower in Group C than in Group K (Table 4).

A significant difference in the total number of doses of ephedrine administered between the two groups was observed (P=0.001) (Figure 1).

Table 1: Episodes of hypotension distribution

Number of episodes of hypotension	Number of parturients (%)	
	Group K	Group C
0	26 (53.10)	7 (14.30)
1	12 (24.50)	10 (20.40)
2	8 (16.30)	21 (42.90)
3	3 (6.10)	8 (16.30)
4	0	1 (2.00)
5	0	2 (4.10)

Table 2: Comparison of mean heart rate (beats/min)

Time after giving drug	Group HR	n	Mean	SD	t	P
1 min	Ketamine	49	87.43	10.16	−2.119	0.037*
	Control	49	91.39	8.23		
3 min	Ketamine	49	85.65	9.03	−2.747	0.007*
	Control	49	90.39	8.00		
5 min	Ketamine	49	85.43	8.71	−3.663	0.001*
	Control	49	91.80	8.50		
7 min	Ketamine	49	87.24	10.10	−2.282	0.025*
	Control	49	91.82	9.73		
9 min	Ketamine	49	87.82	9.84	−4.394	0.001*
	Control	49	96.00	8.55		
11 min	Ketamine	49	85.90	8.87	−3.805	0.001*
	Control	49	92.80	9.07		
13 min	Ketamine	49	85.51	10.04	−2.756	0.007*
	Control	49	91.53	11.54		
15 min	Ketamine	49	84.78	8.77	−2.854	0.005*
	Control	49	89.82	8.71		

* < 0.001 is statistically significant

Table 3: Comparison of mean systolic blood pressure (mmHg)

Time after giving drug	Group SBP (mmhg)	n	Mean	SD	t	P
1 min	Ketamine	49	120.73	9.07	2.212	0.029*
	Control	49	116.69	9.01		
3 min	Ketamine	49	114.12	11.77	2.705	0.008*
	Control	49	107.59	12.12		
5 min	Ketamine	49	108.22	13.45	2.821	0.006*
	Control	49	99.96	15.48		
7 min	Ketamine	49	105.06	16.55	3.173	0.002*
	Control	49	94.73	15.65		
9 min	Ketamine	49	109.39	13.17	4.157	0.001*
	Control	49	98.37	13.07		
11 min	Ketamine	49	110.57	12.11	3.078	0.003*
	Control	49	102.61	13.45		
13 min	Ketamine	49	110.00	12.01	2.372	0.02*
	Control	49	103.20	16.06		
15 min	Ketamine	49	110.16	10.28	0.641	0.523
	Control	49	108.49	15.12		

SBP: Systolic blood pressure, SD: Standard deviation, * < 0.001 is statistically significant

Table 4: Comparison of mean diastolic blood pressure (mmHg)

Time after giving drug	Group DBP (mmhg)	n	Mean	SD	t	P
1 min	Ketamine	49	74.18	8.40	3.865	0.001*
	Control	49	68.20	6.83		
3 min	Ketamine	49	70.96	9.42	3.949	0.001*
	Control	49	63.27	9.86		
5 min	Ketamine	49	66.76	8.51	4.145	0.001*
	Control	49	58.45	11.15		
7 min	Ketamine	49	64.24	11.00	4.523	0.001*
	Control	49	54.00	11.42		
9 min	Ketamine	49	66.94	10.76	3.74	0.001*
	Control	49	58.53	11.49		
11 min	Ketamine	49	66.82	9.23	3.257	0.002*
	Control	49	59.96	11.49		
13 min	Ketamine	49	67.14	9.84	3.185	0.002*
	Control	49	60.16	11.77		
15 min	Ketamine	49	68.00	8.50	1.601	0.113
	Control	49	64.86	10.79		

DBP: Diastolic blood pressure, SD: Standard deviation, * < 0.001 is statistically significant

In this study, the mean APGAR at 1 min and 5 min was comparable in both the groups (Table 5). We observed similar Visual analogue (VAS) scores in both the groups (Figure 2).

A significantly higher incidence of nausea was observed in Group C (73.5%) as compared to Group K (42.9%) with P=0.002. Furthermore, 40.8% in Group C had vomiting and 18.4% in Group K had vomiting, and the difference was statistically significant (P=0.015). The high incidence of nausea and vomiting in Group C may be attributed to hypotension. In Group C, mood changes (hallucinations)

Table 5: Comparison of mean APGAR

Time after giving drug	Group				P
	Group K		Group C		
	Mean	SD	Mean	SD	
APGAR 1 min	8	0	8	0	-
APGAR 5 min	9	0	9	0	-

SD: Standard deviation

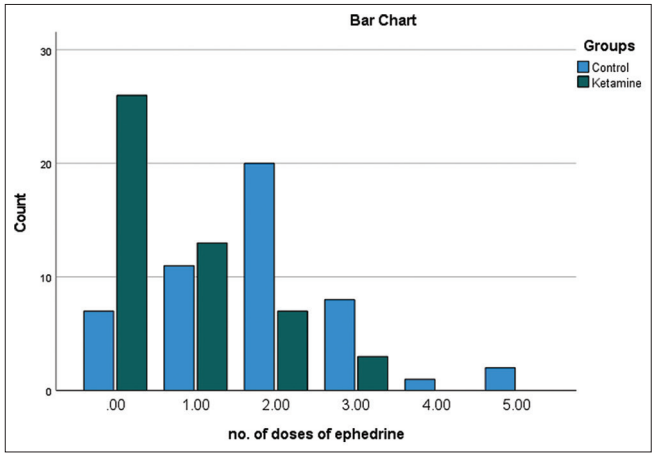

Figure 1: Total number of doses of ephedrine administered

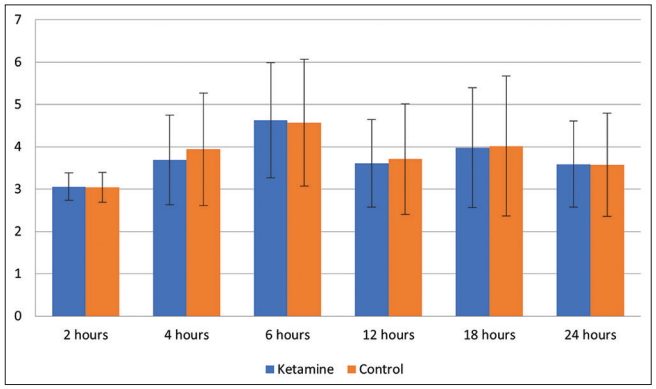

Figure 2: Comparison of mean visual analog scale scores

were noted in 14.28% of parturients, whereas 18.36% of parturients in Group K had mood changes, and the difference was statistically not significant (P=0.585) (Figure 3).

DISCUSSION

Neuraxial techniques are preferred over GA for lower segment cesarean section (LSCS). SA has many advantages over GA.

Advantages in the use of neuraxial anesthesia for cesarean delivery:

- Minimizes exposure of the neonate to maternal anesthetic medications

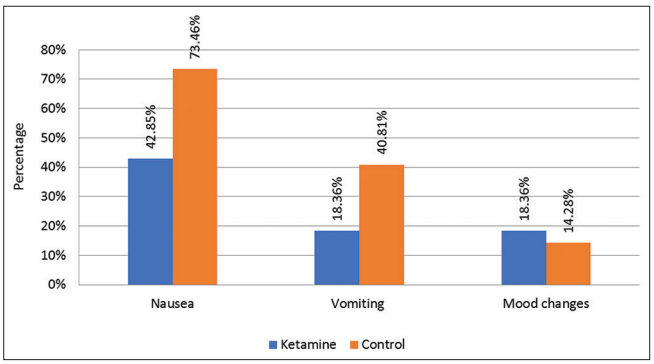

Figure 3: Distribution of adverse events

- Airway manipulation is avoided
- Improves postoperative pain management
- Allows the mother to see the child almost immediately after birth.

However, SA can result in hypotension, which in turn may cause severe undue adverse effects in mothers such as nausea, vomiting, and dizziness. Hypotension may also lead to fetal hypoxia and acidosis, thus affecting both maternal and fetal outcomes. Hence, it is important to identify the parturients having hypotension and promptly treat it.

Decreased vascular resistance due to sympathetic blockade and decreased CO due to peripheral blood pooling in blocked areas of the body is the cause of hypotension after SA in LSCS.[9,10] In addition to that, in pregnancy, women become more sensitive to local anesthetics and less responsive to vasopressors and have lower MAP at term.[3] Hence, parturients are susceptible to develop profound hypotension following central neuraxial blockade for the LSCS.[11]

Peripheral vascular tone is shown to be decreased at term in parturients, especially in multiparous. Decreased peripheral vascular tone results in blood volume being already trapped in the extremities even before SA, and the sympathetic blockade with SA further increases the blood pooling. Therefore, parturients with low baseline vascular tone may be at higher risk of developing hypotension post-SA.[11]

To prevent SA-induced hypotension in parturients, many approaches have been recommended, such as fluid preloading, co-loading, vasopressor agent administration, administration of drugs that affect peripheral vascular resistance, left uterine displacement with placement of wedge under the right buttock, and use of compression stockings. Since the strategies aiming to increase intravascular volume are limited, the use of vasopressor agents has become more and more popular in recent years. However, administration of prophylactic vasopressor agents in parturients may cause undesirable effects on the mother and fetus.

Ketamine has emerged as a unique drug with a wide range of applications, including sedation, analgesia, bronchodilation, and sympathetic nervous system stimulation. It is an optimal anesthetic drug for hypotensive patients as it enhances the release of catecholamines and inhibits their reuptake, hence maintaining vascular resistance and arterial blood pressure. These criteria can help in using ketamine to prevent hypotension that commonly occurs after SA, especially during CS in parturients.[1]

Previous studies have found that the fetus temporarily adapts to lower uterine blood flow by shifting CO to the cerebral cortex. This compensatory reflex, however, is blocked by both intravenous and inhalational anesthetics. Whereas, ketamine does not suppress it due to its propensity to boost maternal BP and uterine blood flow, thus enhancing uterine perfusion. Ketamine when administered to mothers at dosages <2 mg/kg IV does not affect the neonates.[1] The results of the present study showed that neither group's APGAR scores were impacted.

The changes in blood pressure, HR, total ephedrine requirement, and VAS score are explained as follows.

Hypotension

In the present study, 46.93% (23 out of 49 parturients) in the ketamine group had hypotension, whereas 85.71% (42 out of 49 parturients) in the control group had hypotension, and the difference was statistically significant (P=0.001).

Similar results with incidence of hypotension were shown in studies done by Salah and Alansary,[1] where 6 (15%) out of 40 parturients, who had received ketamine, had mild hypotension with no episodes of severe hypotension in any parturients. Whereas, 40 (100%) out of 40 parturients had mild hypotension and 22 (55%) out of 40 parturients had severe hypotension in the placebo group.

In the study done by Hemmingsen C et al.,[8] they compared preoperative intravenous ketamine(0.7mg/kg) vs Fentanyl(1.5mg/kg). They concluded that ketamine is better in controlling hypotension.

In another study by Hassanein and Mahmoud,[12] out of 45 patients, 29 who belonged to the ketamine group had hypotension whereas 38 out of 45 patients belonging to the control group had hypotension and this difference was statistically significant (P=0.02) Menkiti et al.,[13] showed that 13 (40%) out of 28 patients in the control group had hypotension, whereas 10 (33%) out of 28 patients in the ketamine group had hypotension, and this difference was not statistically significant.

HR

In our study, we did not find any difference in baseline heart. However, we found a statistically significantly higher mean HR (P=0.037) among the control group when compared to the ketamine group at 1 min. The results displayed similar results till 15 min (at 3 min, 5 min, 7 min, 9 min, 11 min, and 13 min). At 15 min (P=0.005) and 19 min (P=0.012), 25 min (P=0.01), 35 min (P=0.006), and 40 min (P=0.008), statistics displayed a statistically significantly higher mean HR among the control group when compared to the ketamine group. The explanation for this is the higher incidence of hypotension in the control group and the compensatory rise in the HR.

In contrast to our study, Salah and Alansary[1], in their study, compared the baseline HR and HR at 5, 10, 15, and 20 min after the intrathecal injection and then every 15 min till the end of the operation. They found that HR was significantly higher among the ketamine group at 5, 10, 15, and 20 min. In contrast to our study, Behdad et al.,[14] in their study, found that HR was significantly higher in the ketamine group than the midazolam group.

SBP

In our study, there was more fall in SBP in Group C by the 1st min (P=0.029) which continued (at 3, 5, 7, 9, and 11 min) till the 13th min (P=0.002) as compared to Group K, which was statistically significant. The mean SBP levels were statistically significantly higher among Group C at 40 (P=0.022), 50 (P=0.008), 55 (P=0.002), and 60 min (P=0.048) when compared to the ketamine group. This correlates with the administration of ephedrine due to the hypotension in the control group.

Our results also compare with the study conducted by:

Duggappa et al.,[15] showed that with respect to SBP, there was a significant fall between the 4th and 15th min in the control group which was similar to findings in the control group of our study. Behdad et al.,[14] showed in their study that there were no significant changes in SBP among both of their study group.

DBP

In our study, there was a statistically significant difference in mean DBP between the two groups from the 1st min (P=0.001) which continued (at 3, 5, 7, 9, and 11 min) till the 13th min (P=0.002), with values being lower in Group C than in Group K.

At other time intervals, there was no significant difference. Similar results have been shown by the similar studies conducted by:

Duggappa et al.,[15] in their study, showed that there was a significant difference in DBP between the two groups between the 4th and 25th min, which is similar to our study. Their result is similar to our study. Behdad et al.,[14] showed in their study that there were no significant changes in DBP among both of their study group.

Total ephedrine requirement

In the present study, there was a statistically significant difference in the total number of doses of ephedrine administered between the two groups with P=0.001. Similar results were shown by:

Salah and Alansary[1] showed that the amount of ephedrine used in the ketamine group (0.9±2.2) was statistically significantly lower than that used in the control group (26.3±5.3) with P≤0.001. Hassanein and Mahmoud[12] showed that there was a significant difference between the two groups with regard to total ephedrine administered with P=0.003 (4.5±2.1 in the ketamine group and 8±3.2 in the control group).

Duggappa et al.,[15] showed that the median ephedrine usage was statistically significant (P<0.001). The amount of ephedrine used in this study is lesser than our study. This difference is mainly due to the definition of hypotension in their study being decrease in MAP <65 mm of Hg irrespective of the baseline blood pressure of the parturients. Furthermore, they have taken the median value of the ephedrine usage in both the groups. In our study, the definition for hypotension is decrease of systolic pressure of more than 20% or <90 mmHg.

VAS score

In the present study, there was no statistically significant different mean VAS scores between the ketamine and control groups at different time intervals (P>0.05).

Behdad et al.,[14] showed in their study that the mean of pain scores in the 1st h after cesarean section in the ketamine group (0.78±1.09) was significantly lower than the control group (1.72±1.22; P=0.00).

Limitations of the study

Sample size was not adequate for the present study, hence, more studies need to be done to get conclusive results.

CONCLUSION

We concluded that low-dose ketamine, when used as a premedicant, is an effective agent in preventing post-spinal intraoperative hypotension in parturients undergoing cesarean section delivery.

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