Original Article

Effect of breastfeeding on haemodynamics and consumption of propofol and sevoflurane: A state entropy guided comparative study

Address for correspondence:
Dr. B Bhaskara, Department of Anaesthesiology, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India.
E-mail: drbhaskar.md@gmail.com

B Bhaskara, VP Dayananda, Sudheesh Kannan, RS Raghavendra Rao, R Ramachandraiah

Department of Anaesthesiology, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India

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ABSTRACT

Background and Aims: Unique post-partum endocrine hormone oxytocin secreted during breastfeeding (BF) has amnestic, sedative properties and down-regulates stress responses. This study was done to assess the effect of BF on consumption of propofol, sevoflurane and haemodynamic stability in women. **Methods:** Study was conducted on 120 women aged 20–30 years of American Society of Anesthesiologists I and II physical status scheduled for tubectomy under general anaesthesia who were randomly allocated to three groups 40 of each; BF, withhold feeding (WF), and non-feeding (NF) groups. All received standard premedication. Heart rate (HR), mean arterial pressure (MAP) and state entropy (SE) values were recorded at regular intervals. All patients were induced with intravenous propofol until the SE levels dropped to 45, and dose of propofol recorded. Airway was secured with laryngeal mask airway and anaesthesia was maintained with sevoflurane in 60% N_2O and O_2. Sevoflurane concentration was adjusted to maintain SE between 40 and 60. End tidal concentration of sevoflurane and consumption of sevoflurane (ml) was recorded by GE Datex-Ohmeda S/5™ System. Results were analysed by analysis of variance and Chi-square test. **Results:** Demographic parameters were comparable. Dose of propofol and sevoflurane consumption in group BF was significantly reduced by 20% and 35%, respectively ($P < 0.05$) compared to group NF. Intra-operative HR and MAP were persistently low in group BF and elevated in group WF ($P < 0.05$). **Conclusion:** BF before induction of anaesthesia decreases the consumption of propofol, sevoflurane and maintains the intra-operative haemodynamic stability, whereas withholding BF increases propofol and sevoflurane consumption with intra-operative higher HR and MAP, compared to control group.

Key words: Breastfeeding, entropy, oxytocin, propofol, sevoflurane, tubectomy

INTRODUCTION

Oxytocin (OT) is a maternal hormone with effect on uterine contraction and milk ejection. More recently, OT has been shown to influence a wide spectrum of behavioural, physiological and endocrine functions mediated through receptors within the brain.[1-4] OT induces several anti-stress-like effects; decrease in heart rate (HR), blood pressure and levels of stress hormones.[5] It increases nociceptive thresholds through enhancement of endogenous opioids.[6,7] Administration of low dose OT can induce anxiolytic-like effect and in higher doses sedative effect.[8] However, very few studies have explored the role of OT on anaesthetic and analgesic consumption. This study was conducted to determine the effect of OT secreted during breastfeeding (BF) on consumption of propofol and sevoflurane and assessment of its effect

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on intra-operative haemodynamics as the secondary outcome.

METHODS

Before commencing this single blind prospective study, approval was obtained from the Institutional Review Board. About 120 women with American Society of Anesthesiologists physical Status I and II, aged 20–30 years, who had uncomplicated pregnancy, delivered full-term, healthy infants by the vaginal route and scheduled for tubectomy were enrolled for the study between July 2014 and December 2014. Parturients with a history of cerebrovascular disease, hypertension, diabetes mellitus and other endocrine disorders, treatment with psychoactive medication, anticipated difficult airway, parturients on sedatives or analgesics and weighing <70% or more than 130% of ideal body weight were excluded from the study. Thorough pre-anaesthetic check-up of all patients including routine investigations was carried out. Tablet ranitidine 150 mg was given early in the morning before surgery. The procedure was explained to the patient and written informed consent was taken.

The parturients were allocated to three groups of 40 each depending on their lactation status. Lactating women were randomly allocated to either BF group or withhold feeding (WF) group based on computer-generated randomisation technique (www.random.org), whereas non-lactating women were considered for the control group (non-feeding [NF]). The BF group (n = 40) consisted of lactating women who breastfed just before induction of anaesthesia. WF group (n = 40) included lactating women who withheld BF for 4 h before induction of anaesthesia.NF group (control) (n = 40) included non-lactating women (coming for interval tubectomy) who had delivered more than a year back and stopped BF on their own for a minimum of 4 weeks before surgery. The details of randomisation were kept with the principal investigator and not revealed to other investigators until the end of the study.

The anaesthesiologist monitoring the patient intra-operatively and post-operatively was not aware of the lactation status of the women or their group allocation; none of the cases were primigravida. On arrival in the operating room, patients were monitored for HR, blood pressure and oxygen saturation by continuous electrocardiogram, non-invasive blood pressure and pulse oximetry, respectively, and basal parameters were recorded. Depth of anaesthesia was monitored by entropy analysis (Entropy module, Datex-Ohmeda S/5 Avance™ workstation, GE Healthcare). Patients were started on intravenous (IV) infusion of Ringer's Lactate solution solution premedicated with injection midazolam 1 mg IV, injection glycopyrrolate 0.2 mg IV, injection fentanyl 2 μg/kg IV and preoxygenated with 100% oxygen for 3 min. Anaesthesia was induced with IV Propofol 10 mg increments injected over 5 s, at 10 s intervals until the state entropy (SE) levels dropped to 45, total dose of propofol required to achieve SE 45 was recorded, and airway secured with laryngeal mask airway-Classic (LMA™) (as per manufacturer's recommendations), and patients were maintained on assisted spontaneous ventilation. If more than 2 attempts were required for LMA insertion, cases were excluded from the study and were managed as per standard institutional protocol. Additional doses of propofol 10 mg were administered as necessary when SE values increased to more than 60 during LMA insertion, and the amount of supplemental propofol used was noted. Anaesthesia was maintained with sevoflurane in 60% N_2O and O_2, with ventilation adjusted to maintain end-tidal CO_2 between 35 and 40 mmHg. Sevoflurane concentration was set at 2% initially and adjusted subsequently to maintain SE levels between 40 and 60, and the difference between response entropy (RE) and SE <10. If the difference between RE and SE exceeded 10, additional doses of fentanyl 1 μg/kg was administered. Fresh gas flow rate was set at 4 l/min for initial 5 min and then reduced to 2 l/min. Sevoflurane and N_2O were discontinued at the end of closure of abdomen and LMA removed after complete recovery. Patients were monitored in the post-operative period for 6 h.

HR, mean arterial pressure (MAP), $EtCO_2$, SE and RE were recorded at baseline, at induction and every 5 min after LMA insertion until 15 min into post-operative period. End-tidal concentration of sevoflurane was recorded at 5 min intervals from the time of LMA insertion until discontinuation of anaesthetics. Parameters recorded were total duration of surgery, duration of anaesthesia, duration of sevoflurane use, total dose of propofol consumed and total volume of sevoflurane consumed (obtained by the anaesthesia gas module of GE Datex-Ohmeda S/5™ Anaesthetic Delivery Unit System).

Sample size was calculated based on findings of a pilot study conducted in our institute involving ten lactating women. The average end-tidal sevoflurane concentration was 1.45 ± 0.32. Keeping the power of study at 80%

and confidence limits at 95%, to detect a minimum of 15% difference in sevoflurane consumption between groups, assuming normal distribution of values in both groups, the minimum sample size required was thirty in each group, we included forty patients in each group for better validation of results. Descriptive and inferential statistical analysis have been carried out in this study. Analysis of variance has been used to find the significance of study parameters between three or more groups of patients, Student's *t*-test (two-tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (inter-group analysis) on metric parameters. Chi-square or Fisher exact test has been used to find the significance of study parameters on a categorical scale between two or more groups. The results were expressed as mean ± standard deviation. $P < 0.05$ was considered statistically significant. The statistical software, namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment version 2.11.1 (IBM, USA) were used for the analysis of the data and Microsoft Word and Excel were used to generate graphs, tables, etc.

RESULTS

A total of 120 patients were included in the study with 40 in each group. Demographic parameters were comparable in all the groups [Table 1]. The mean duration of the surgery, mean duration of anaesthesia and mean duration of sevoflurane use were comparable between the three groups [Table 1].

Post-partum day distribution [Table 2] in lactating women were comparable among the BF group and WF group ($P = 1.0$).

Baseline HR [Figure 1] was comparable in all the three groups (*P*-0.4); intraoperatively, a significant increase in HR was observed in WF group compared to other groups at all-time points until post-operative period ($P < 0.001$), BF group had lower HR throughout the procedure compared to other groups ($P < 0.001$).

Baseline MAP [Figure 2] was comparable in all the three groups (*P*-0.1), MAP was persistently higher in WF group compared to other groups ($P < 0.001$) and BF group had lower and stable MAP throughout the procedure compared to other groups ($P < 0.001$).

SE [Figure 3] values were comparable at baseline and throughout the procedure among all the groups.

The difference in requirement of propofol [Table 3] to reach SE 45 was statistically significant in BF and

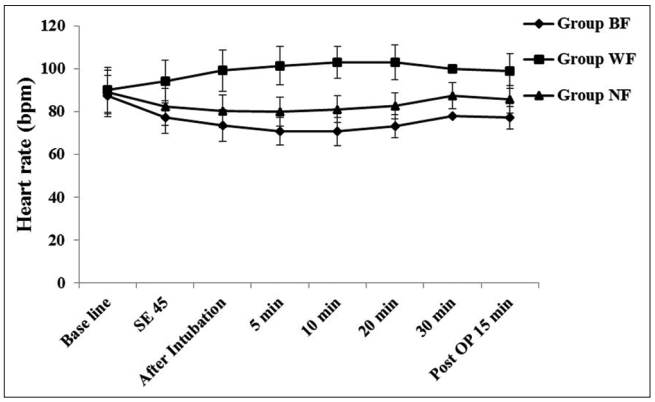

Figure 1: Comparison of heart rate (bpm). Changes in heart rate (mean ± standard deviation): Baseline (pre-induction); at induction (state entropy 45); after intubation; at 5, 10, 25, 30 and 15 min post-extubation

Table 1: Patient demographics

Patient demographics	Group BF	Group WF	Group NF	*P*
Age in years (mean±SD)	29.10±2.67	29.05±2.57	29.60±1.92	0.530
Weight (kg) (mean±SD)	60.70±5.14	59.48±3.66	60.60±5.87	0.475
Duration of anaesthesia (min) (mean±SD)	23.00±3.43	22.23±2.57	21.85±5.49	0.430
Duration of sevoflurane use (min) (mean±SD)	17.75±2.93	18.05±2.42	16.95±4.38	0.319
Duration of surgery (min) (mean±SD)	19.83±3.08	19.70±2.60	18.63±5.27	0.310

BF – Breastfeeding; WF – Withhold feeding; NF – Non-feeding; SD – Standard deviation

Table 2: Post-partum week distribution in lactating women (breastfeeding, withhold feeding groups)

Post-partum days	Group BF		Group WF	
	n	Percentage	*n*	Percentage
0-3	2	5.0	3	7.5
4-6	38	95.0	37	92.5
Total	40	100.0	40	100.0

BF – Breastfeeding; WF – Withhold feeding

Table 3: Comparison of propofol and sevoflurane usage

Propofol and Sevoflurane usage	Group BF	Group WF	Group NF	*P*
Total dose of propofol (mg) (mean±SD)	74.13±6.97	102.88±5.30	95.25±8.00	<0.001**
Propofol consumed per kg (mg/kg) (mean±SD)	1.22±0.05	1.73±0.04	1.58±0.08	<0.001**
Total sevoflurane consumed (ml) (mean±SD)	3.80±0.76	6.43±0.75	5.15±0.77	<0.001**
Average end tidal concentration of sevoflurane (%) (mean±SD)	1.41±0.11	2.19±0.58	1.85±0.36	<0.001**

**Highly significant. SD – Standard deviation; BF – Breastfeeding; WF – Withhold feeding; NF – Non-feeding

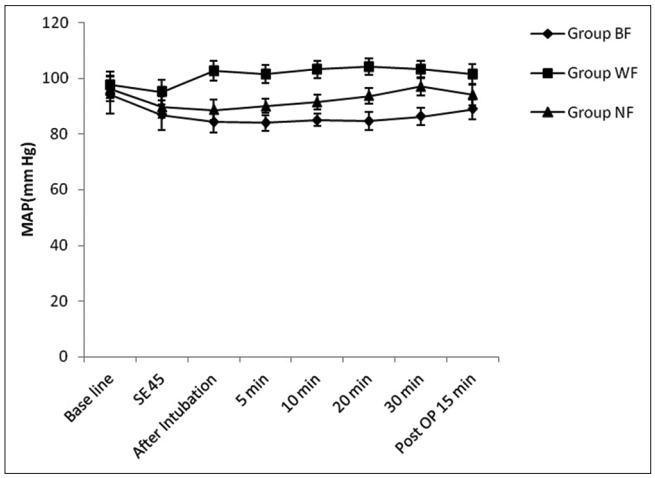

Figure 2: Comparison of mean arterial pressure (mm Hg) in three groups of patients studied changes in mean arterial pressure (mean ± standard deviation); Baseline (pre-induction); at induction (state entropy 45); after intubation; at 5, 10, 25, 30 and 15 min post-extubation; (SE 45 - State entropy 45, MAP - Mean arterial pressure)

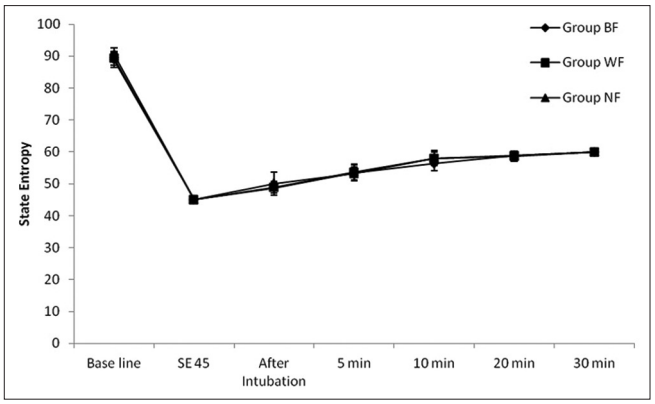

Figure 3: Comparison of state entropy values. State entropy: Baseline (pre-induction); at induction (state entropy 45); after intubation; at 5, 10, 25 and 30; (SE 45 - State entropy 45)

WF groups when compared to control group, and requirement was highest (102.88 ± 5.30 mg) in WF group and least (74.13 ± 6.97 mg) in BF group. None of the patients required additional doses of propofol during insertion of LMA.

The difference in requirement of sevoflurane [Table 3] to maintain anaesthesia was statistically significant in BF and WF groups when compared to control group, requirement was highest (6.43 ± 0.75 ml) in WF group and least (3.80 ± 0.76 ml) in BF group. The average end-tidal concentration of sevoflurane was significantly lower in BF group and higher in WF group compared to group NF ($P < 0.001$). *Post-hoc* analysis between groups with regards to propofol and sevoflurane consumption showed statistically significant difference between groups NF, BF and WF, respectively.

DISCUSSION

In the current study, the effect of OT which is secreted during BF on haemodynamics and anaesthetic drug consumption was determined. OT is mainly produced and synthesised in magnocellular neurons of the hypothalamic paraventricular (PVN) and supraoptic nuclei and secreted into the periphery via the posterior neurohypophysis. OT is also produced in parvocellular neurons within the PVN, and these neurons project to many areas within the brain such as other hypothalamic nuclei, the median eminence, amygdala, hippocampus, locus coeruleus, striatum, raphe nuclei, the dorsal motor nucleus of the vagus nerve (DMX) and nucleus tractus solitarii (NTS). In addition, oxytocinergic fibres project down to the spinal cord, where they terminate on the presynaptic neurons of the sympathetic chain in the intermediolateral cell column and also in the dorsal horn in the area where pain modulation takes place.[9] The central actions of the OT are mediated via OT receptors (OTR) which are distributed widely in the central nervous system (CNS). Until date, only one OTR is identified which is a member of Class 1 G protein-coupled receptor family.[10]

During physiological and psychological stress responses, oxytocinergic neurons are activated, particularly in PVN of the hypothalamus and secreted into the circulating blood.[11]

OT induces several anti-stress-like effects such as decrease in HR, blood pressure and the levels of stress hormones,. These effects of OT are probably mediated through the hypothalamus and the vagal nuclei (DMX and NTS).[5] Increase in OT release from the hypothalamus inhibits hypothalamic-pituitary-adrenal (HPA) axis by acting at three different levels.[12] First, peripheral OT acts on the adrenal gland to inhibit corticosteroid secretion. Legros *et al*.[13] demonstrated that human males treated with exogenous OT followed by synthetic adrenocorticotropic hormone (ACTH) showed a blunted response in cortisol secretion, suggesting that exogenous OT inhibits corticosteroid synthesis in the adrenal gland. Second, Neumann *et al*.[14] demonstrated that peripheral OT inhibits ACTH release from the pituitary gland. They injected exogenous corticotrophin-releasing factor (CRF) into lactating rats and measured ACTH responses, finding a reduction in ACTH response. Third, central OT has

inhibitory effects on the hypothalamic CRF activation. Intracerebroventricular injection of synthetic OT decreased CRF mRNA responses to physical stress.[3]

The earlier study conducted on humans showed that BF women had significantly lower hormonal stress responses (as evident by lower cortisol and ACTH) during exercise stress than non-BF mothers and women without children.[15] Several follow-up studies have detected lower cardiovascular markers of stress (as evidenced by lower basal systolic blood pressures, higher levels of cardiac parasympathetic control and modulation of HR reactivity) during the task in breastfeeders as compared with non-BF mothers and women without children.[16] Light *et al*.[17] found similar cardiovascular patterns for BF mothers during the anticipation of the public-speaking stressor; it is possible that any stress-buffering effects of BF are more potent during the immediate BF period. However, Born *et al*.[18] have shown that intranasal administration of OT, which passed directly into the brain, suppressed cortisol response to psychological stress, as well as attenuated emotional functions after stress episodes, indicating in humans, the inhibitory effect of OT on HPA activity mediated through CNS in addition to peripheral effect. However, short-term IV administration of OT to women to enhance uterine contractions or decrease blood loss during labour or caesarean delivery confirms its effect in decreasing blood pressure.[19] This hypotensive response to OT is due to decreases in total vascular resistance despite compensatory increases in HR, stroke volume and cardiac output. Grewen *et al*.[5] tested 28 early post-partum mothers, obtaining multiple blood samples for OT, the sympathetic marker, norepinephrine (NE) and the lactation hormone, prolactin while monitoring their cardiovascular responses to two stressors. They observed that greater overall OT level was related to lower plasma NE and higher Prolactin levels; in contrast, higher NE was linked to increases in HR and decreases in stroke volume. These data support a cardioprotective role for OT, which may influence the magnitude and haemodynamic determinants of cardiovascular stress responses. Similar findings were observed in our study, with women receiving anaesthesia immediately after BF showing a better haemodynamic profile compared to those who withheld BF and NF women.

The anxiolytic-like effect seems to be mediated within the amygdala, which is richly provided with OTRs, during BF, there may also be increased CNS gamma-amino butyric acid, a major inhibitory neurotransmitter, which may inhibit the affective state and behaviour of the lactating animal.[20] It was observed that administration of OT can induce both anxiolytic-like effects and in higher doses, sedative effects.[8] The possibility that raised OT levels during parturition alters cognition was also investigated. The results suggested there was temporary impairment although there was no correlation between OT levels and cognitive performance.[21] The evidence that OT impairs some memory-related tasks has led to suggestions that it has a role in the forgetting of delivery pain in mothers.

Analgesic effect has been linked to the periaqueductal grey and the dorsal horn of the spinal cord.[6,7] OT increases nociceptive thresholds through an enhancement of endogenous opioids. The release of opioid peptides is stimulated by OT neurotransmission. Classical studies have demonstrated that chronic OT treatment induced not only anti-stress effects but also analgesia; this analgesic effect was blocked by the opioid antagonist naloxone but not by an OT antagonist, indicating that OT increases endogenous opioid transmission.[6] The above-described physiological properties of OT may have contributed to decreased requirement of induction dose of propofol and maintenance dose of sevoflurane in this study in women who breastfed just before induction of anaesthesia.

Plasma levels of OT normally vary between 10 and 100 pg/ml. OT secretion peaks during child birth and during BF, levels returning to normal in between BF.[22] Blunting of plasma stress hormone levels were seen up to 30 min after BF, and BF women did not have attenuated physiological or subjective anxiety responses to a laboratory psychosocial stress administered 1 h after their last episode of lactation.[16,23] This may be the reason for the higher requirement of sevoflurane and propofol in women in whom BF was withheld. The possible rebound increase in noradrenaline levels following OT-induced temporary suppression may explain higher HR and MAP in these women, practice implication of this concept include the possibility that the withhold feeding mother might be physiologically more fragile and more susceptible to post-partum illness, further research is required to provide sufficient evidence for this effect.[24] When OT levels are measured in the cerebrospinal fluid, levels 5–10 fold higher than in plasma are normally found, but the concentration of OT at its receptor sites is not known. OT does not readily cross into the brain and needless to say, blood levels often do not correlate well

with brain levels, so measuring peripheral OT may not correlate levels at OTR within the CNS.[25,26]

In humans, minimum alveolar concentration (MAC) is reduced by 30% during early gestation, and in post-partum women MAC returns to that of the non-pregnant state within 2 days of delivery, possibly due to sedative effect of progesterone which returns to baseline within 24–48 h after delivery.[27] Post-partum, gastrointestinal tract related and mechanical factors are relieved immediately after delivery, gastric emptying time returns to normal as early as 18 h post-partum and gastric volume and pH are comparable with non-pregnant women.[27,28] All cases in our study were elective and were fasting overnight and received acid aspiration prophylaxis; no signs of acid aspiration (gastric contents/stain on LMA at extubation time) were seen in our cases, but it is recommended to use LMA-proseal™ in post-partum period.

The present findings in lactating women were restricted to after 3 days and within 1st week after giving birth, and we could not compare with exclusive formula feeding mothers to confirm if the same associations occur in these groups. As these data are suggestive rather than conclusive, further research is required to provide sufficient evidence on effects of OT parse on the requirement of anaesthetic and non-anaesthetic drugs.

CONCLUSION

The results of this study indicate that BF before induction of anaesthesia attenuates the stress response to surgery and maintains haemodynamic stability, and reduces the consumption of both propofol and sevoflurane, and with-holding of BF increases the stress response with increased consumption of both propofol and sevoflurane.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Announcement

CALENDAR OF EVENTS OF ISA 2016

The cut off dates to receive applications / nominations for various Awards / competitions 2016 is as below. Hard copy with all supportive documents to be sent by Regd. Post with soft copy (Masking names etc.) of the same by E Mail to secretaryisanhq@gmail.com. The masked soft copy will be circulated among judges. Only ISA members are eligible to apply for any Awards / competitions. The details of Awards can be had from Hon. Secretary & also accessed from www.isaweb.in

Cut Off Date	Name of Award / Competition	Application to be sent to
30 June 2016	Bhopal Award for Academic Excellence	Hon. Secretary, ISA
30 June 2016	Late Prof. Dr. A. P. Singhal Life Time Achievement Award	Hon. Secretary, ISA
30 June 2016	Rukmini Pandit Award	Hon. Secretary, ISA
30 June 2016	Dr. Y. G. Bhoj Raj Award	Hon. Secretary, ISA
30 Sept. 2016	Kop's Award	Chairperson, Scientific Committee ISACON 2016 with Copy to Hon. Secretary, ISA
30 Sept. 2016	Prof. Dr. Venkat Rao Oration 2017	Hon. Secretary, ISA
30 Sept. 2016	Ish Narani Best poster Award	Chairperson, Scientific Committee ISACON 2016
30 Sept. 2016	ISA Goldcon Quiz	Chairperson, Scientific Committee ISACON 2016
10 Nov. 2016	Late Dr. T. N. Jha Memorial & Dr. K. P. Chansoriya Travel Grant	Hon. Secretary, ISA, copy to Chairperson Scientific Committee of ISACON 2016
20 Oct. 2016	Awards (01 Oct 2015 to 30 Sept 2016) 1. Best City Branch 2. Best Metro Branch 3. Best State Chapter 4. Public Awareness – Individual 5. Public Awareness – City / Metro 6. Public Awareness - State 7. Ether Day (WAD) 2016 City & State 8. Membership drive 9. Proficiency Awards	Hon. Secretary, ISA
20 Oct. 2016	ISACON 2018 Bidding	Hon. Secretary, ISA

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