

# Hepatic resection is associated with reduced postoperative opioid requirement

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## Abstract

**Background and Aims:** Postoperative pain can significantly affect surgical outcomes. As opioid metabolism is liver-dependent, any reduction in hepatic volume can lead to increased opioid concentrations in the blood. The hypothesis of this retrospective study was that patients undergoing open hepatic resection would require less opioid for pain management than those undergoing open pancreaticoduodenectomy.

**Material and Methods:** Data from 79 adult patients who underwent open liver resection and eighty patients who underwent open pancreaticoduodenectomy at our medical center between January 01, 2010 and June 30, 2013 were analyzed. All patients received both general and neuraxial anesthesia. Postoperatively, patients were managed with a combination of epidural and patient-controlled analgesia. Pain scores and amount of opioids administered (morphine equivalents) were compared. A multivariate linear regression was performed to determine predictors of opioid requirement.

**Results:** No significant differences in pain scores were found at any time point between groups. Significantly more opioid was administered to patients having pancreaticoduodenectomy than those having a hepatic resection at time points: Intraoperative ( $P = 0.006$ ), first 48 h postoperatively ( $P = 0.001$ ), and the entire length of stay (LOS) ( $P = 0.002$ ). Statistical significance was confirmed after controlling for age, sex, body mass index, and American Society of Anesthesiologists physical status classification (adjusted  $P = 0.006$ ). Total hospital LOS was significantly longer after pancreaticoduodenectomy ( $P = 0.03$ ). A multivariate linear regression demonstrated a lower opioid consumption in the hepatic resection group ( $P = 0.03$ ), but there was no difference in opioid use based on the type of hepatic resection.

**Conclusion:** Patients undergoing open hepatic resection had a significantly lower opioid requirement in comparison with patients undergoing open pancreaticoduodenectomy. A multicenter prospective evaluation should be performed to confirm these findings.

**Key words:** Abdominal surgery, liver resection, opioid metabolism, opioid-related adverse events, pancreaticoduodenectomy, postoperative pain control

## Introduction

In the United States, approximately 80% of patients experience severe pain after surgery.<sup>[1]</sup> Patients with higher

levels of postoperative pain tend to have more postoperative complications, longer hospital stays leading to higher medical costs, and lower levels of patient satisfaction.<sup>[2,3]</sup>

The purpose of this retrospective study was to test the hypothesis that patients undergoing open hepatic resection require less

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opioid to manage postoperative pain than those undergoing open pancreaticoduodenectomy (Whipple procedure). This hypothesis was based on the fact opioids are subjected initially to either oxidation or hydrolysis by cytochrome P450 enzymes and then conjugated to hydrophilic molecules for excretion. Any reduction in hepatic volume, therefore, can lead to an increased opioid concentration in the blood resulting in greater opioid bioavailability.<sup>[4]</sup>

## Material and Methods

This study was approved by the Institutional Review Board. The study population included all adult patients who underwent open hepatic resection or open pancreaticoduodenectomy at our institution between January 01, 2010 and June 30, 2013. Patients included in the study received a combination of general and neuraxial (epidural) anesthesia. Patients included in the study were identified by current procedural terminology codes. Their medical record numbers were then used to access the patients' information from the electronic health record (EHR). The records contained: The patient's medical history, diagnoses, procedures performed, medications administered, patient condition, pain scores, and laboratory values. Doses of preoperative and post-Intensive Care Unit (ICU) medications administered to patients were acquired from the electronic medication administration record. All intraoperative information, including medication dosing and type of surgical procedure, was obtained from the electronic anesthesia record. Information pertinent to epidural anesthesia was obtained from the acute pain database. Patient's pain scores were documented in the postanesthesia care unit (PACU)/ICU nursing electronic record. Information regarding ICU care, including the length of stay (LOS) and medications administered, was acquired from the ICU medical record. All records are component parts of the patient's EHR. Opioid doses were converted to morphine equivalents using an online calculator (GlobalRPH, <http://www.globalrph.com/narcoticonv.htm>).

## Statistical analysis

Statistical analysis was performed using SAS® 9.3 software (SAS Institute, Cary, NC). The Student's *t*-test was used to analyze differences in continuous variables between the two groups: age, body mass index (BMI), total hospital LOS, total ICU LOS, total length of surgery, total opioid administered during entire hospitalization, total preoperative opioid administered, total intraoperative opioid administered, total postoperative opioid administered during the first 48 h, and total postoperative acetaminophen administered during the first 48 h. A Chi-square test was used to test for differences in categorical variables between the two groups: gender and American Society of Anesthesiologists (ASA) physical status classification. To determine predictors of

opioid requirement, a multivariate analysis was performed by adjusting a linear regression model of total opioid (in morphine equivalents [mg]) administered postoperatively during the first 48 h against gender, age, ASA status, BMI, and type/extent of liver resection. Univariate summary statistics and frequencies were analyzed for all variables of interest. The value of  $P < 0.05$  was used to indicate significance.

## Results

Two hundred and ninety-two patients were identified that met inclusion criteria. After further evaluation, data from several patients were excluded from the study.

Data from 159 patients were included in the final analysis in our study, eighty patients having had open pancreaticoduodenectomy and 79 patients having had open hepatic resection [Figure 1].

The study population in the pancreaticoduodenectomy group included 62 patients with primary pancreatic carcinoma, three patients with pancreatic metastases, eight patients with a cystic pancreatic lesion, four patients with neuroendocrine tumors, and three patients with duodenal carcinoma. The study population in the hepatic resection group included 22 patients with primary hepatic/cholangiocarcinoma, 38 patients with liver metastases, nine patients with a hepatic cyst, two with echinococcal cysts, and eight patients with an adenoma or hemangioma. Three patients in the resection group had early stage cirrhosis with normal coagulation that did not preclude use of neuraxial anesthesia. Of the 79 patients who underwent a hepatic resection, three had wedge resections, 41 had resections greater than a wedge but less than hemihepatectomy, five had

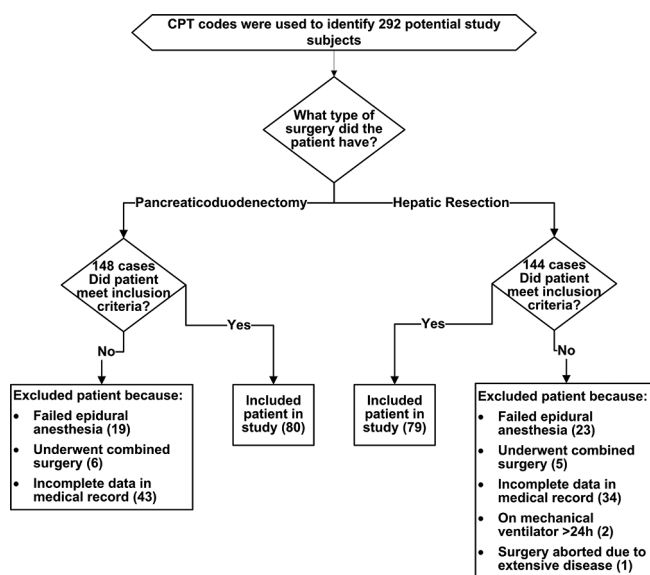


Figure 1: Study population

a left hemihepatectomy, 16 had a right hemihepatectomy, and 12 had resections greater than a hemihepatectomy. The size of resection was not defined in two patients.

### Surgical technique

Open pancreaticoduodenectomy and the majority of hepatic resections were performed primarily through an upper midline incision. A small number of hepatic resections were performed through a right subcostal incision. For both types of cases, fixed retraction was achieved with the use of a Thompson retractor (Thompson Surgical Instruments, Traverse City, MI, USA).

### Anesthetic technique

Before induction of anesthesia, all patients received a thoracic epidural catheter placed at the T6–T8 level. Midazolam (0.5–1 mg) and fentanyl (50–100 mcg) were administered intravenously prior the procedure. Ropivacaine 0.2% only or bupivacaine 0.125% + 10 mcg hydromorphone/ml was administered using a CADD (Smits Medical ASD Inc., St. Paul, MN, USA) infusion pump. A bolus of infusion medication (4–6 ml) was administered before surgical incision and followed by a continuous epidural infusion of the same solution at 4–8 ml/h. Epidural anesthesia was managed intraoperatively by the anesthesiologist and postoperatively by members of the acute pain team.

The intraoperative bupivacaine: ropivacaine ratio was 13:67 in the pancreaticoduodenectomy group and 14:65 in the hepatic resection group. Epidural infusions were continued postoperatively for 3 days. The postoperative bupivacaine:ropivacaine ratio was 33:47 in the pancreaticoduodenectomy group and 29:50 in the hepatic resection group. The most common reason that, postoperatively, ropivacaine was changed to bupivacaine + hydromorphone was hypotension. In the combination infusion, the bupivacaine concentration was lower when compared to when ropivacaine was used as the sole agent (0.125% vs. 0.2%). The addition of hydromorphone allowed the use of a reduced dose of local anesthetic. Bupivacaine was changed to ropivacaine if lower extremity weakness impaired mobilization.

Fentanyl was administered intraoperatively (50 mcg increments) only if patients demonstrated signs of pain (tachycardia or hypertension). Hydromorphone was administered to all patients at the end of the procedure (0.4–0.8 mg based on patient weight).

### Postoperative pain management

Postoperatively, in either the PACU or ICU, hydromorphone boluses (0.4–0.8 mg based on patient weight) were administered by the nursing staff. All study participants were managed with an epidural infusion at rate of 4–8 ml/h for 3 days. After removal of

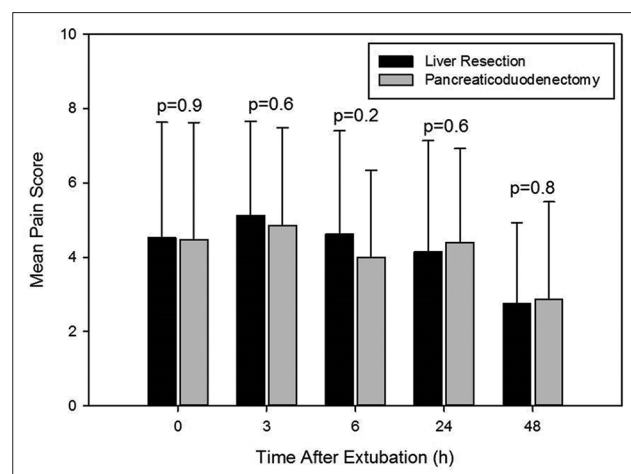
the epidural catheter, patient-controlled analgesia (PCA) using an Alaris infusion pump (CareFusion Corporation, San Diego, CA, USA) was initiated. PCA settings included 0.2 mg of hydromorphone with a lockout time of 6 min and a maximal dose of 2 mg in 1 h. The PCA pump was set without a basal rate. The usual duration of PCA was 3–5 days. Breakthrough pain was managed with PRN morphine. All opioids administered were included in the statistical analysis. Postoperatively, both groups received intravenous acetaminophen as needed. Pain intensity was evaluated with an 11 point numerical rating scale (scores 0–10). Pain scores were recorded postoperatively at multiple time points by the bedside nurse in the patient care setting (PACU, ICU, and floor). Hour 0 was defined as the time of patient admission to the PACU or when the patient was extubated. Postoperative pain scores at 0, 3, 6, 24, and 48 h were obtained from the EHR. For statistical evaluation, all opioid doses administered were converted to morphine equivalents.

### Demographics

There was no difference in ASA classification or BMI between groups. The liver resection group was younger and had more females ( $P = 0.003$  and  $0.03$ , respectively). Fourteen patients (17.7%) in the liver resection group and 15 patients (18.8%) in the pancreaticoduodenectomy group received preoperative opioids, but no statistically significant difference was demonstrated after dose conversion to morphine equivalents ( $P = 0.8$ ). Length of surgery for pancreaticoduodenectomy was significantly longer than for hepatic resection ( $P = 0.0001$ ) [Table 1].

### Postoperative evaluation

No statistically significant differences were found in postoperative pain scores at 0, 3, 6, 24, and 48 h between the two groups [Figure 2].



**Figure 2:** Postoperative pain in patients undergoing liver resection and those undergoing pancreaticoduodenectomy

A significantly larger amount of opioids was administered to patients having pancreaticoduodenectomy than for patients having hepatic resection. This difference was demonstrated intraoperatively ( $P = 0.006$ ), in the first 48 h after surgery ( $P = 0.001$ ), and for the entire hospital stay ( $P = 0.002$ ) [Table 2]. The difference in opioid consumption in the first 48 h remained statistically significant after adjustment for age, sex, BMI, and ASA classification (adjusted  $P = 0.006$ ). Twenty-three patients (28.8%) in the pancreaticoduodenectomy group and 9 (11.4%) in the hepatic resection group received intravenous acetaminophen postoperatively in the first 48 h. The overall acetaminophen dose was significantly lower in the hepatic resection group ( $P < 0.0001$ ) [Table 1]. The pancreaticoduodenectomy group had a significantly longer average total hospital LOS as compared to the hepatic resection group (8.7 vs. 7.0 days, respectively [ $P = 0.03$ ]). There was, however, no difference in the ICU LOS. The lower opioid consumption in the hepatic resection group in the first 48 h postoperatively was confirmed in the multivariate linear regression analysis ( $P = 0.03$ ). There was no statistically significant difference between the amount of opioids used for the different types of hepatic resections [Table 3].

## Discussion

In this study, we were able to confirm our hypothesis that patients undergoing open hepatic resection have significantly

reduced postoperative opioid requirements in comparison with patients undergoing open pancreaticoduodenectomy. Both procedures, pancreaticoduodenectomy and hepatic resection, are major abdominal surgery with identical or very similar surgical incisions and perioperative anesthetic management. Patients in both groups had combined general and neuraxial anesthesia. The majority of patients in both groups had malignancies which are associated with significant pain and frequently accompanied with chronic opioid administration.<sup>[5-7]</sup>

Our findings demonstrated lower opioid use in the hepatic resection group coincident with no statistically significant difference in pain scores between groups for the first 48 h postoperatively. The explanation for this reduced postoperative opioid use is most likely multifactorial, but increases in blood opioid concentration due to a reduction in liver volume, and therefore metabolic capacity, likely plays an important role. In fact, hepatic volume reduction has been demonstrated to result in increased opioid bioavailability.<sup>[8-10]</sup> A capacity for compensation by increased metabolism in the kidney and intestine has been demonstrated.<sup>[8,11]</sup> This compensation can be expected in patients with a chronic liver disease but not acutely after hepatic resection.<sup>[10]</sup> This study also demonstrates that the intraoperative opioid requirement of patients having hepatic resection was significantly lower in comparison to the pancreaticoduodenectomy group. This finding is most likely

**Table 1: Demographic and perioperative data: Comparison between groups**

Variables	Hepatic resection (n=79) (%)	Pancreaticoduodenectomy (n=80) (%)	P
BMI (kg/m <sup>2</sup> )	28.3±5.25	27.8±6.6	0.62
Age (years)	58.0±14.0	64.6±13.2	0.003
Males	36 (45.6)	50 (62.5)	0.03
Females	43 (54.4)	30 (37.5)	
ASA II	14 (18.2)	9 (11.3)	0.3
ASA III	58 (75.3)	62 (77.5)	0.8
ASA VI	5 (6.5)	9 (11.3)	0.3
Preoperative use of opioids (mg)	11.6±11.02	12.7±14.75	0.8
Duration of surgery (min)	322±122	496±113	0.0001
Postoperative use of acetaminophen (mg)	1119±1912	3554±2061	0.0001
Hospital LOS (days)	7.0±4.9	8.7±4.5	0.03
ICU LOS (days)	1.3±0.9	1.4±1.1	0.6

The values are expressed as mean±SD and analyzed using unpaired t-test or numbers (%) and analyzed using Chi-square test. BMI = Body mass index, LOS = Length of stay, ICU = Intensive Care Unit, SD = Standard deviation, ASA = American Society of Anesthesiologist

**Table 2: Total opioids in morphine equivalents given intra- and post-operatively in the postanesthesia care unit/ Intensive Care Unit and during total hospital stay in liver resection and pancreaticoduodenectomy cohorts**

Variables	Liver resection (n=79)		Pancreaticoduodenectomy (n=80)		P
	Mean±SD	95% CI	Mean±SD	95% CI	
Intra-operatively	39.2±21.9	34.3-44.1	50.8±29.5	44.3-57.4	0.006
PACU/ICU	55.1±55.9	42.5-67.6	84.6±89.5	64.8-104.6	0.001
Total hospital stay	94.3±64.1	79.9-108.7	135.5±95.4	114.3-156.8	0.002

PACU/ICU = Postanesthesia care unit/Intensive Care Unit, SD = Standard deviation, CI = Confidence interval

**Table 3: Factors associated with opioids requirement multivariate linear regression analysis**

Variables	Morphine equivalents (mg)	SE	P
Hepatic resection	-48.7 <sup>†</sup>	22.7	0.03
Pancreaticoduodenectomy	0 <sup>‡</sup>	-	-
Females	-17.3	13.0	0.2
Males	0	-	-
Age	-2.1	0.5	0.0001
BMI	1.7 <sup>§</sup>	1.1	0.1
ASA II	3.1	28.3	0.9
ASA III	12.9	23.2	0.6
ASA IV	0	-	-
Wedge resection	13.2	49.6	0.8
Resection greater than wedge resection	2.3	23.9	0.9
Left hemihepatectomy	-5.9	40.2	0.9
Resection greater than hemihepatectomy	-30.5	30.8	0.3
Right hemihepatectomy	0	-	-

<sup>†</sup>Negative values indicate decreased requirement of opioids in comparison to reference category, <sup>‡</sup>Positive values indicate increased requirement of opioid in comparison to reference category, <sup>§</sup>0 values indicate reference categories. Pancreaticoduodenectomy is a reference group for hepatic resection group, right hemihepatectomy is a reference group for comparison of different types of hepatic resections age and BMI were used as continuous predictors. SE = Standard error, BMI = Body mass index, ASA = American Society of Anesthesiologist

related to the fact that the duration of hepatic resections, on average, was significantly shorter.

There are two primary mechanisms for opioid metabolism: oxidation via the cytochrome P450 system and glucuronidation. It has been demonstrated that despite the fact that glucuronidation is less affected by liver disease, the final bioavailability of substances undergoing glucuronidation can be very high and thus, the use of opioids that undergo oxidative metabolism is potentially safer in patients with liver dysfunction.<sup>[4]</sup> Commonly used opioids are metabolized differently in the liver. Fentanyl, a short-acting opioid, is metabolized by oxidation to norfentanyl and other inactive metabolites.<sup>[12]</sup> Morphine, on the other hand, is metabolized by glucuronidation to morphine-3-glucuronide (55%) (an inactive compound), morphine-6-glucuronide (10%) (an active compound), normorphine (4%) (a compound with minimal activity), and codeine.<sup>[13]</sup> Hydromorphone is also metabolized by glucuronidation and although its metabolites do not have significant analgesic activity, they are responsible for central effects similar to those produced by morphine-6-glucuronide.<sup>[12-14]</sup> The effects of all opioids can be more pronounced in patients with concomitant renal impairment.<sup>[12-14]</sup>

Our study also demonstrates a decreased use of acetaminophen in the liver resection group. Considering the hepatic metabolism of this medication, a higher bioavailability of acetaminophen can also be suggested. The decreased use

of acetaminophen in the liver resection group might also be due to decreased prescribing due to the concern for hepatic toxicity.<sup>[15]</sup> It has been recommended to reduce the maximum dose of acetaminophen in patients with impaired hepatic function to 2 g/day.<sup>[16]</sup> In general, the use of nonsteroidal anti-inflammatory drugs is not recommended in patients with cirrhosis or renal insufficiency.<sup>[16]</sup> It is important to note that only three patients in the hepatic resection group had early stage cirrhosis that was unlikely to have significantly affected the metabolism of medications.

In this study, three of 79 patients in the hepatic resection group had either a wedge resection or multiple wedge resections, resulting in minimal liver volume reductions. The majority of patients in the hepatic resection group (96%) had larger resections, most likely resulting in significant alterations in opioid metabolism. Rudin *et al.*, in a prospective study, compared morphine pharmacokinetics in patients undergoing either hepatic or colon resection.<sup>[10]</sup> In the liver resection group, the volume of hepatic tissue removed was between 15% and 85%. They demonstrated that postoperatively, patients having a hepatic resection had a significantly higher plasma morphine concentration ( $P < 0.01$ ) and significantly lower morphine clearance ( $P < 0.01$ ) than patients in the colon resection group. In addition in their study, blood morphine concentrations on postoperative day 1 correlated significantly with the volume of liver resected (Spearman's  $r = 0.6$ ,  $P < 0.02$ ). The authors also demonstrated an inverse correlation between the ratios of morphine-6-glucuronide (active metabolite): morphine ( $r = -0.45$ ,  $P = 0.03$ ) and morphine-3-glucuronide (inactive metabolite): morphine ( $r = -0.52$ ,  $P = 0.04$ ) with the volume of liver resected. This study also demonstrated that hepatic resection patients more frequently experienced sedation and respiratory depression, particularly if more than 50% of liver volume was removed. These findings clearly confirm that opioid metabolism is significantly reduced after liver resection. Beebe *et al.* described opioid-related respiratory depression in two donors after living donation of the right hepatic lobe. This was likely related to decreases in hepatic opioid metabolism.<sup>[17,18]</sup> In this study, two patients in the hepatic resection group and none in the pancreaticoduodenectomy group were excluded from data collection due to the need for mechanical ventilation for more than 24 h postprocedure. Both patients had significant hepatic resections: (extended right hemihepatectomy and resection of segments 7 and 8). Both patients also had a relatively low BMI (20 kg/m<sup>2</sup> and 29 kg/m<sup>2</sup>) and received significant doses of opioids in the first 24 h (436 mg and 268 mg of morphine equivalents). After extensive review of the medical records, we concluded that relative opioid-related respiratory depression was the reason for prolonged ventilation.

Although our study demonstrated a significant difference in opioid use between hepatic and nonhepatic (Whipple) resection, our investigation did not show a relationship between the size of hepatic resection and amount of opioids used. This is likely because the study was not powered for this analysis. This association, however, has been described in previous investigations.<sup>[10,19]</sup>

It has been demonstrated that female, obese, and younger patients report both greater postsurgical pain after abdominal surgery and chronic pain in general.<sup>[20,21]</sup> There was no statistical difference in BMI between groups in our study, but the pancreaticoduodenectomy cohort had more males and was, on average, older. Despite these demographic differences, the hepatic resection group in our study demonstrated decreased total opioid use. This generally indicates less perceived pain.

In this study, patients undergoing pancreaticoduodenectomy had longer total hospital LOS in comparison to patients after hepatic resection. The cause of this is likely multifactorial. One possible explanation is that increased opioid use is associated with increased adverse effects related to relative opioid overdose.<sup>[22-26]</sup> Patients in the pancreaticoduodenectomy group in our study also underwent an extensive gastrointestinal resection. They likely needed longer to return to their normal eating habits as compared to hepatic resection patients.

Effective perioperative pain management is extremely important not only in regards to a patient's quality of life, but also as it can affect their outcome. Inadequate pain control after major surgery is associated with a number of significant complications as well as increased mortality.<sup>[27,28]</sup> High quality pain management helps prevent the surgical stress and organ dysfunction seen with major surgery.<sup>[29]</sup>

This study has several limitations. The single center retrospective nature of this evaluation can be associated with selection bias and unrecognized confounders. In addition, the level of evidence obtained in a retrospective evaluation is inferior compared to prospective randomized trials. Despite the fact that our patient's preoperative pain scores were not available, we were able to determine that their preoperative opioid consumption did not differ between groups.

## Conclusion

Our investigation has demonstrated that hepatic resection is associated with reduced opioid requirement. Aggressive use of opioids in this patient population can potentially lead to significant complications, primarily related to relative opioid overdosing. Taking into consideration the retrospective design of our study, further multicenter prospective pharmacokinetic

studies should be performed to determine the association between the amount of liver tissue resected and opioid bioavailability.

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Nil.

## Conflicts of interest

None declared.

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## Conference Calendar July 2016

Name of conference	Dates	Venue	Name of organising Secretary with contact details
European Society of Regional Anaesthesia 35 <sup>th</sup> Annual Congress 2016 (ESRA 2016)	September 7 <sup>th</sup> -10 <sup>th</sup> , 2016	6229 GV MECC Maastricht. The Netherlands	<a href="http://www.esra2016.com/">http://www.esra2016.com/</a> CONGRESS VENUE MECC Maastricht Address: Forum 100, 6229 GV Maastricht Telephone: +31 (0)43 38 38 383 Email: <a href="mailto:info@mecc.nl">info@mecc.nl</a>
Annual East Zone Conference of ISA ISACON EAST – 2016	September 9 <sup>th</sup> -11 <sup>th</sup> , 2016	Puri, Odisha	Dr. Debaprasad Mohanty Mobile No.: +91-9437021313 <a href="mailto:drdev07@yahoo.com">drdev07@yahoo.com</a>
ISACON UP – 2016 Annual State Conference of ISA UP State Chapter	September 9 <sup>th</sup> -11 <sup>th</sup> , 2016	Corbett National Park, Nainital	Org Secretary: Dr. R. K. Bhaskar Mobile No.: +91-9837027227 Email: <a href="mailto:rkbhasker@gmail.com">rkbhasker@gmail.com</a>
ISACON MP 2016 30 <sup>th</sup> Annual State Conference of ISA MP State Chapter	September 10 <sup>th</sup> , 2016	Hotel Jabali Palace, Jabalpur	Org Secretary: Dr. Ashish Sethi Mobile No.: +91-9826168747 Email: <a href="mailto:ashsethi64@yahoo.com">ashsethi64@yahoo.com</a> Website: <a href="http://www.isampchapter.com">http://www.isampchapter.com</a>
Society For Airway Management 19 <sup>th</sup> Annual Meeting 2016 (SAM 2016)	September 15 <sup>th</sup> -18 <sup>th</sup> 2016	Atlanta, Georgia, USA	<a href="http://samhq.com/2014-sam-meeting-in-seattle-washington/">http://samhq.com/2014-sam-meeting-in-seattle-washington/</a> The Society for Airway Management is a 501(c)(3) organization 5753 Tanager Street   Schererville, IN 46375 PH: (773) 834-3171   FAX: (773) 834-3166 Administrator: <a href="mailto:amprince@peds.bsd.uchicago.edu">amprince@peds.bsd.uchicago.edu</a> Webmaster: <a href="mailto:webpagesam@gmail.com">webpagesam@gmail.com</a>
7 <sup>th</sup> National Airway Conference NAC 2016	September 16 <sup>th</sup> -19 <sup>th</sup> 2016	Vadodara	Dr. Amit Shah Organizing Chairman Dr. Apeksh Patwa Organizing Secretary Contact: Dr. Dinesh Patel Telephone : 9879925025 Email Id: <a href="mailto:nac2016vadodara@gmail.com">nac2016vadodara@gmail.com</a> Website: <a href="http://www.nac2016.in">http://www.nac2016.in</a>
ISACON AP – 2016 25 <sup>th</sup> Annual State Conference of ISA AP State Chapter	September 16 <sup>th</sup> -18 <sup>th</sup> 2016	Tanish Function Hall, Kurnool, AP	Org Secretary: Dr. G. Shantiraju Mobile No.: +91 7702228107 9494491910 Email: <a href="mailto:gunnasraj@gmail.com">gunnasraj@gmail.com</a> Website: <a href="http://www.isaaccon2016.in/">http://www.isaaccon2016.in/</a>