ORIGINAL ARTICLE

Comparison of clonidine versus midazolam in monitored anesthesia care during ENT surgery– A prospective, double blind, randomized clinical study

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ABSTRACT

Background: Monitored anaesthesia care (MAC) typically involves administration of local anaesthesia in combination with IV sedatives, anxiolytic and/or analgesic drugs which is a common practice during various ENT surgical procedures.

Aims: To compare the effectiveness and safety profile of clonidine against midazolam as an intravenously administered agent for MAC.

Settings and design: Randomized, double blind, prospective study.

Methodology: Sixty patients undergoing ENT surgery under MAC were divided into two groups of 30 patients each. The patients in Group C received clonidine 2 mcg/kg IV and in Group M received midazolam 20 mcg/kg IV over 10 min. Ramsay sedation score, requirement of intraoperative rescue sedation (propofol) and analgesic (diclofenac infusion), postoperative visual analogue score & analgesic requirement (tramadol), adverse effects, recovery profile (Aldrete Score) and satisfaction scores of patients and surgeon were recorded. Data were analysed by chi-square, student t test and analysis of variance using Epi info 6 with p value < 0.05 as significant.

Results: Mean Ramsay sedation score (RSS) was significantly more in Group M (2.50 ± 0.73) as compared to Group C (1.80 ± 0.85), $p = 0.001$. Intraoperative rescue sedation with propofol infusion (if RSS < 3) was required by significantly higher number of patients in Group C (n=19, 63.4%) than in Group M (n=6, 20%), P=0.001. Intraoperative rescue analgesic requirement was significantly more in Group M (n =21, 70%) as compared to Group C (n=11, 36.6%), p=0.009. Intraoperative bleeding score was significantly less in Group C (1.93 ± 0.80) than in group M (2.43 ± 0.73), P=0.014. Postoperative VAS score was also significantly less in Group C than in Group M (2.28 ± 1.9 vs. 3.28 ± 1.81, P=0.041). Both patients and surgeon were more satisfied in Group C than in Group M (p=0.010 & 0.019 respectively). All patients had Aldrete score of 10 at the end of surgery in both groups.

Conclusion: We conclude that clonidine along with rescue sedation using propofol infusion can be a better alternative to midazolam in MAC since it provides a calm patient with better intraoperative & postoperative analgesia, and a bloodless surgical field leading to increased satisfaction of both patient and surgeon.

Key Words: Monitored anaesthesia care; Clonidine; Midazolam; ENT surgery; Bleeding

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INTRODUCTION

Monitored anaesthesia care (MAC) may be applied for various ENT surgeries in which an adequate sedation and analgesia without respiratory depression are desirable for comfort of both the patient and the surgeon.[1] In order to reduce the incidence of complications, it is important to have a bloodless surgical field as far as possible for better visibility. Bleeding control is usually attained with local application of epinephrine.[2] Pain during surgery may lead to sympathetic stimulation and a restless patient may have tachycardia and hypertension, leading to increased bleeding in the surgical field.[3,4]

Several drugs have been used for sedation during surgery under local anaesthesia with monitored anaesthesia care including propofol, benzodiazepines and opioids[5]. However, propofol may cause oversedation and disorientation,[6] benzodiazepines may result in confusion, particularly in elderly[7] and opioids are associated with increased risk of respiratory depression and oxygen desaturation[8]. All of these untoward effects may hamper patient's cooperation during surgery[9] and would make these agents less than ideal for the intraoperative management of sedation in MAC. Midazolam is the most frequently used sedative and has been reported to be well tolerated when used in MAC.[1,10]

Alpha-2 adrenoreceptors agonists i.e. clonidine and dexmedetomidine have been recently used perioperatively for their sedative, analgesic, sympatholytic and cardiovascular stabilizing effects with reduced anaesthetic requirements.[11] Clonidine offers beneficial pharmacological properties producing dose dependent sedation, analgesia, anxiolysis without relevant respiratory depression.[12] It decreases sympathetic outflow and has been reported to reduce bleeding significantly in ENT surgeries.[13,14]

No study is available from Indian subcontinent about the use of intravenous clonidine for MAC as an alternative to standard midazolam sedation. Therefore, we designed a randomized double blind study to compare the effect of intravenous clonidine versus midazolam on sedation, analgesia and surgical bleeding in monitored anaesthesia care with local anaesthesia in ENT surgeries.

METHODOLOGY

After institutional Ethics Committee approval, informed consent was taken from each patient for this randomized, double-blind clinical trial. Adult cooperative patients between ages of 18 to 60 yrs., scheduled for elective ENT surgery under local anaesthesia like tympanoplasty, myringoplasty, dacryocystorhinostomy, functional endoscopic sinus surgery, epulis, septoplasty, polypectomy etc. were included in this study. Exclusion criteria were raised serum urea and creatinine, advanced liver disease (liver enzymes twice the normal range or higher), history of chronic use of sedatives, narcotics or both, history of alcohol or drug abuse, or allergy to any of the study medications. Using a computer-generated randomization schedule, 60 patients were randomly divided in two groups of 30 each to receive either clonidine (Group C) or midazolam (Group M) for sedation during surgery. To maintain double blind nature of the study, drugs were prepared by an anaesthesia technician and diluted to a fixed volume of 10ml. The anaesthesiologist who gave the study drug and recorded data was also blind to the patient group assignment.

Standard monitoring including ECG, noninvasive BP, and pulse oximetry was applied to the patient and baseline vitals were recorded. Local anaesthesia was given by the operating surgeon, who was unaware of the group allocation, using lidocaine 2% with adrenaline 1:200,000. Group C patients received clonidine 2 mcg/kg IV and group M patients received midazolam 20 mcg/kg IV over 10 min. After that, Ramsay Sedation Score (RSS) was assessed. Target sedation level was defined as RSS $\geq$ 3. If RSS was less than 3, rescue sedation with propofol 100-300 mcg/kg/hr IV was given. Then surgeon proceeded to perform the surgery under local anaesthesia. Whenever patient complained of pain during the surgery, diclofenac 75mg infusion was given as rescue analgesic and the surgeon used an additional dose of local anaesthetic. Heart rate (HR), mean arterial pressure (MAP), respiratory rate, peripheral oxygen saturation (SpO_2) were recorded every 5 min till 60 min. Intraoperative bleeding was assessed by bleeding scale (0-4), acceptable bleeding score being 0-2.

After completion of the surgery patients were shifted to the recovery room. There, postoperative pain was assessed using Visual Analogue Scale (0-10cm); if VAS was >3, analgesia was provided with i.v. tramadol 100 mg. Aldrete score was assessed in recovery room every 5 min, till score of 10 was achieved. Time to achieve Aldrete score of 10 was noted, which was the criterion to shift the patient to the ward. Patients were asked to answer the question, 'How would you rate your experience with the sedation (or analgesia) you have received during surgery?' using a 7-point Likert verbal rating scale. This assessment of patient's satisfaction with sedation and analgesia was performed just before shifting to ward to minimize the effects of sedation on patient's judgement. Moreover, the surgeons were asked to rate their satisfaction with operative conditions, using the same scale at the end of surgery, accept-

able satisfaction score of both the patient and surgeon being 5-7. All adverse events like bradycardia (HR <60 beats/min), hypotension (MAP <60 mmHg sustained for >10 min), respiratory depression (respiratory rate ≤ 10 bpm), oxygen desaturation ($SpO_2 < 92\%$), nausea, vomiting or unplanned hospital admission etc were recorded. Various scores used in the study are shown in Appendix 1.

Sample size was calculated based on a difference of 2 in patient's satisfaction scores with sedation between groups, a population variance of $(2)^2$, a two-sided α of 0.05, and a power of 90%. The number of patients required in each group to demonstrate a difference between groups was 30. Results were expressed as number of occurrences, percentage and mean $\pm$ SD. Demographic characteristics, preoperative vitals were compared using student's 't' test and nominal data were compared with chi square test. Repeated measures analysis of variance was used to compare continuous variables. Statistical analysis was performed using Epi info 6 and MS Excel. A p value less than 0.05 was considered significant.

Appendix I: Various scores used in the study

A. **Sedation scale (Ramsay Sedation Scale) is as follows:**

1. Anxious, agitated or restless
2. Cooperative, oriented and tranquil
3. Responds to command
4. Asleep but has a brisk response to light glabellar tap or loud auditory stimulus
5. Asleep has a sluggish response to a light glabellar tap or loud auditory stimulus
6. Asleep no response

B. **Intraoperative bleeding scale**

0 - No bleeding
1 - Slight bleeding; no suctioning of blood required
2 - Slight bleeding; occasional suctioning required. Surgical field not threatened.
3 - Slight bleeding; frequent suctioning required. Bleeding threatened surgical field a few seconds after suction was removed.
4 - Moderate bleeding; frequent suctioning required. Bleeding threatened surgical field directly after suction was removed.

C. **Likert Scale**

1	2	3	4	5	6	7
Extremely dissatisfied	Dissatisfied	Somewhat dissatisfied	Undecided	Somewhat satisfied	Satisfied	Extremely satisfied

D. **Post Anaesthesia Recovery Score (Modified Aldrete Score)**

Parameter	Score		
	2	1	0
Activity	Moves all extremities voluntarily or on command	Moves two extremities voluntarily or on command	Unable to move extremities
Respiration	Breathes deeply and coughs freely	Dyspnoeic, shallow or limited breathing	Apnoeic
Circulation	BP ± 20 mm of preanaesthetic level	Bp ± 20-50 mm of preanaesthetic level	BP ± 50 mm of preanaesthetic level
Consciousness	Fully awake	Arousable on calling	Not responding
Oxygen saturation	SpO_2 >92% on room air	Supplemental O_2 required to maintain SpO_2 >90%	SpO_2 <90% with O_2 supplementation
Total Score=10; A score of ≥9 required for discharge			

E. **Visual Analogue Scale VAS (0-10cm)**

0	2	4	6	8	10

No pain Worst pain

RESULTS

Both groups were comparable regarding demographic characteristics, type and duration of surgery, baseline values of mean arterial pressure(MAP), heart rate (HR), respiratory rate (RR) and peripheral oxygen saturation (SpO_2) ($p > 0.05$) (Table 1).

Table 1 - Demographic characteristics

Variables	Group C	Group M	P Value
Age(year)	40.37±14.07	33.83±13.55	0.071
Weight(Kg)	55.63±5.83	55.03±9.11	0.762
Sex			
Male	15(50%)	14(46.66%)	0.796
Female	15(50%)	16(53.33%)	

[Data are expressed as mean ± SD or number (%)]

Regarding intragroup variations, mean HR and MAP showed a significant fall from baseline ($p = 0.000$) in Group C, whereas they showed a significant rise from baseline ($p = 0.000$) in Group M. On intergroup comparison mean HR and MAP were significantly less in Group C as compared to Group M ($p = 0.000$) (Fig1&2). However, none of the patients in both the groups had any episode of bradycardia (HR < 60/min), tachycardia (HR > 120/min), hypotension (SBP < 90mmHg) or hypertension (SBP > 140mmHg). No significant change was observed in respiratory rate and SpO_2 in both the groups ($p > 0.05$).

Target sedation level (Ramsay sedation score ≥ 3) was achieved by significantly higher number of patients in Group M (80%, n = 24) as compared to Group C (36.6%, n = 11). Mean Ramsay sedation score was also significantly more in Group M (2.50 ± 0.73) as compared to Group C (1.80 ± 0.85),$p = 0.001$. Therefore rescue sedation with propofol infusion, to achieve target sedation score was required by significantly less number of patients in Group M (20%, n = 6) than in Group C (63.4%, n = 19), $p = 0.001$ (Table 2).

In spite of better sedation in Group M, intraoperative rescue analgesic (diclofenac infusion) was required by significantly more number of patients in Group M (n = 21, 70%) than in Group C (n = 11, 36.6%), $P = 0.009$. Postoperative VAS score was also significantly less in group C (2.28 ± 1.9) than in Group M (3.28 ± 1.81), $P = 0.041$. Postoperatively, tramadol was required by 11 (36.66%) patients in Group C and 18 (60%) patients in Group M, $p = 0.07$. All these patients required intraoperative rescue analgesic (Table 2).

Acceptable bleeding score (0, 1, 2) was achieved by a higher number of patients in Group C (n = 25, 83.3%) as compared to Group M (n = 13, 43.3%), $P = 0.051$. Intraoperative bleeding, as suggested by mean bleeding score, was also significantly less in Group C (1.93 ± 0.80) than in Group M (2.43 ± 0.73), $P = 0.014$ (Fig 3, 4).

Acceptable satisfaction score, (achievement of score of 5-7 on Likert Scale) was reported by 28 (93.33%) patients in Group C and 24 (80%) patients in Group M, $p = 0.129$. Surgeon also reported acceptable satisfaction in 25 (83.33%) cases in Group C as compared to 19 (63.33%) cases in Group M, $p = 0.08$. Mean satisfaction scores of patients and surgeons were significantly more in Group C than in Group M indicating that both

Table 2: Comparison of baseline vital signs, type and duration of surgery in both groups

Variables	Group C	Group M	P Value
Heart Rate(bpm)	96.50± 18.597	91.67± 19.866	0.335
Mean Arterial Pressure (mmHg)	100.90±13.27	96.97±9.342	0.189
Respiratory Rate (pm)	18.23±3.664	17.84±2.874	0.648
SpO_2 (%)	97.77±1.755	98.17±1.744	0.379
Type of Surgery			
Myringoplasty	7(23.33%)	5(16.66%)	0.563
Functional Endoscopic Sinus Surgery	8(26.66%)	3(10%)	0.131
Dacryocystorhinostomy	5(16.66%)	4(13.33%)	0.738
Tympanoplasty	7(23.33%)	9(30.0%)	0.617
Septoplasty	3(10.0%)	7(23.33%)	0.205
Polypectomy	0(0%)	1(03.33%)	0.318
Epulis	0(0%)	1(03.33%)	0.318
Duration of Surgery(min)	56.67±6.06	54.83±8.66	0.344

[Data are expressed as mean ± SD or number (proportion)]

Table 3: Comparison of Sedation score, Pain score, and requirement of rescue sedative and analgesics in two groups.

Variables	Group C	Group M	P Value
Ramsay Sedation Score (RSS) n(%)			
1	9 (30%)	2 (6.66%)	
2	10 (33.33%)	4 (13.33%)	
3.	11 (36.66%)	24 (80%)	
Ramsay Sedation Score (Mean ± SD)	1.80±0.85	2.50±0.73	0.001
Intraoperative rescue sedation (if RSS = 1,2) n(%)	19(63.33%)	6 (20.00%)	0.001
Intraoperative rescue analgesic (if VAS>3) n(%)	11(36.6%)	21(70.00%)	0.009
Postoperative VAS n(%)			
0	9 (30%)	4 (13.4%)	
1	0 (0%)	0 (0%)	
2	10 (33.4%)	6 (20%)	
3	0 (0%)	2 (6.6%)	
4	9 (30%)	13 (43.4%)	
5	0 (0%)	1 (3.4%)	
6	2 (6.6%)	4 (13.4%)	
Postoperative VAS (Mean ± SD)	2.28±1.91	3.28±1.81	0.041
Postoperative rescue analgesic (if VAS>3) n(%)	11 (36.6%)	18 (60%)	0.07

patients and surgeons were more satisfied in clonidine group as compared to midazolam group (P=0.010 & P=0.019 respectively) (Fig 3, 4).

After surgery when the patients were shifted to recovery room, all patients in both the groups had an Aldrete score of 10, showing complete recovery and were eligible for shifting to ward. There were no perioperative adverse effects seen in any patient in both the groups.

DISCUSSION

Monitored Anaesthesia Care (MAC) is a technique of combining local anaesthesia with parenteral drugs for sedation and analgesia.[15] A common practice with sedation is that the sedative drug is given in larger doses in an attempt to achieve a calm, pain free patient[16]. Since the approval of midazolam by FDA in 1985,[17] practitioners of all medical disciplines embraced the versatility provided by midazolam though the risk of losing airway control, hypoxia and hypotension with higher doses of midazolam has also been recognised. With the recent development of highly specific α_2 agonists clonidine and dexmedetomidine, there has been a renewed interest in this class of drugs for use in perioperative period[18,19] as they offer both sedation, analgesia and can provide induced hypotension with a bloodless surgical field.[20] Use of oral clonidine,[13,21] intravenous clonidine[22] and dexmedetomidine [23,24] had been investigated in ENT surgeries conducted under general anaesthesia with promising results; however use of clonidine as an alternative to midazolam for MAC is not much analysed.

We compared the use of intravenous clonidine and midazolam premedication in MAC for ENT surgeries conducted under local anaesthesia. We found that mean Ramsay Sedation Score (RSS) was significantly more in midazolam group than in clonidine group. Rescue sedation with propofol infusion to achieve target sedation level (Ramsay score of 3) was required by significantly higher number of patients in clonidine group as compared to midazolam group (63.4% vs 20%). Higher sedation levels with midazolam as compared to clonidine have also been reported earlier.[25] A progressive increase in sedation occurs with increasing dose of clonidine. For better sedation effect bolus dose of clonidine should be followed by continuous IV infusion 1-4 mcg/kg/h.[26] Infusion was not given in our study and this could be the reason for increased requirement of rescue sedation in clonidine group. In contrast, intraoperative sedation was found comparable in midazolam and dexmedetomidine groups,[27,11] since dexmedetomidine is 8 times more potent than clonidine and infusions were given following bolus dose in these studies.

Midazolam causes sedation by GABA receptor activation.[28] α_2 receptors are found densely in the

pontine locus ceruleus which is an important source of sympathetic nervous system innervations of the forebrain and a vital modulator of vigilance. The sedation effects evoked by α_2 agonists most likely reflects inhibition of this nucleus.[29] Clonidine has been shown to produce analgesia to experimental pain stimuli after systemic injection.[30] Central α_2-adrenoceptors in the dorsal horn of the spinal cord are likely involved in this effect.[31] Midazolam could reduce pain perception by producing sedation, causing amnesia and its anxiolytic effect could reduce the emotional component of pain.[32] Anxiety and pain are intimately related in that anxiety leads to an exacerbation of pain.[33]

We observed that intraoperative rescue analgesic requirement was significantly less in clonidine group (36.6%) than in midazolam group (70%), $p=0.009$. Postoperative VAS score was also significantly less in clonidine group than in midazolam group. Better analgesic effect of α_2 agonists has been demonstrated in other studies too.[11,20,34] However, clonidine was not found effective in reducing moderate to severe postoperative pain of tonsillectomy.[25]

Intraoperative bleeding was significantly less in clonidine group as compared to midazolam group in present study, as reported earlier.[11,14,35] Similarly, Jabalameli et al[13] found that number of patients in the clonidine group with bleeding score of 3 and 4 (bleeding threatening surgical field) were less than in placebo group, ($P<0.05$) reinforcing our findings. Controlled hypotension effectively reduces surgical blood loss and improves surgical conditions.[36] Clonidine facilitates controlled hypotension by decreasing the heart rate, systolic, diastolic and mean blood pressure.[37] Clonidine and dexmedetomidine both are found effective in reducing bleeding in ENT surgeries.[21,24,38] Haemodynamic attenuation produced by clonidine, resulting from diminished sympathetic outflow by central α_2 adrenoceptor stimulation may contribute to reduced bleeding.[39] We also observed that mean heart rate and mean arterial pressure were significantly lower from baseline at various time intervals in clonidine group than midazolam group as demonstrated by others.[11,21,22,40]

Intravenous midazolam and clonidine usually don't produce significant changes in respiratory rate, minute ventilation, SpO_2 and $EtCO_2$,[26,41,42] which is similar to our observations. However, higher doses of midazolam have been reported to reduce peripheral oxygen saturation, that has been attributed to hypoventilation and higher respiratory rates were observed as a compensatory response to maintain ventilation.[11,27]

In the present study, both patients and surgeons were significantly more satisfied in clonidine group. Although midazolam produces faster onset of sedation but the quality of sedation, acceptance of steal induction and parental satisfaction in children were reported to be better with clonidine than midazolam.[43,44] Clonidine produces sedation by decreasing the sympathetic nervous system activity, resulting in a calm patient that can be easily aroused to full consciousness.[29] Additional analgesic property of α_2 agonists also contributes to higher patient satisfaction rate in clonidine group[27]. Surgeons were more satisfied in clonidine group since α_2 agonists have the ability to provide bloodless surgical field[11,35,38] and interruption of surgery by patients' complaint of pain requiring rescue analgesic was also less in clonidine group in our study.

When clonidine and midazolam were compared, no difference had been reported regarding time from the end of surgery to discharge readiness and actual discharge[22,25] as supported by the present study, in which all the patients in both groups had modified Aldrete score of 10 immediately after surgery. Contrary to this, delayed readiness for recovery room discharge with dexmedetomidine compared to midazolam have been found that could be attributed to sustained therapeutic plasma concentration of dexmedetomidine which was likely to be present on arrival at recovery room as it has an elimination half life of about 2 hr and drug infusion was continued upto the end of surgery in that study.[27]

Clonidine premedication is considered to be safe without episodes of hypotension, bradycardia, low oxygen saturation, nausea, vomiting [25] as has been observed in our study. Although the reported complications associated with clonidine and midazolam are few, they are clinically important and should be kept in mind.

Limitations of our study were firstly, inclusion of a broad variety of ENT surgeries for the study, since the number of a single type of procedure like middle ear surgery or sinus surgery to be performed under local anesthesia in our institution, would not have been sufficient to satisfy the required sample size of 30 per group as revealed by the power analysis. Secondly, we used IV clonidine as a bolus not followed by infusion; hence target sedation level for MAC (Ramsay sedation score ≥ 3) was achieved by using propofol infusion in 63% cases in clonidine group. The reason for this being, intravenous clonidine, as premedication was used for first time in MAC for ENT surgeries lasting for ≤ 1 hour in our institution; we were not sure about its safety profile so we used it as a bolus dose only, as used by some authors previously,[13,25,40] and in a relatively lower dose (2mcg/kg)[45]. In a dose finding

study, Marinangeliaf et al[46] demonstrated that, when sedation and analgesic effect of clonidine is required, 3 mcg/kg bolus dose followed by a continuous infusion of 0.3 mcg/kg per hour has to be considered the optimal intravenous dose. The higher dose of intravenous clonidine (5mcg/kg) produced better analgesia but the degree of hypotension and sedation was more severe and longer lasting, which required ephedrine administration and careful monitoring of the patient. Inspite of the above limitations certain conclusions can be drawn from our study.

CONCLUSION

We conclude that, as compared to conventional premedication with midazolam (20 mcg/kg IV) for monitored anaesthesia care in ENT surgeries performed under local anaesthesia, intravenous clonidine (2mcg/kg IV bolus) with rescue sedation using propofol infusion could be a better alternative, since it provides a calm patient with better intraoperative & postoperative analgesia, and a bloodless surgical field leading to increased satisfaction of both patient and surgeon.

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Professor Joseph Drew Tobias, MD joins APICARE

We are pleased to announce that Professor Joseph Drew Tobias, MD has joined editorial board of Anaesthesia, Pain & Intensive Care.

Professor Tobias is currently the Chairman, Department of Anesthesiology & Pain Medicine, Attending Physician, Cardiothoracic Intensive Care Unit, Nationwide Children's Hospital; and Professor of Anesthesiology & Pediatrics, The Ohio State University, Columbus, Ohio (USA). He earned his MD as well as Bachelor of Arts (Biology) diplomas from University of Missouri - Kansas City School of Medicine, Kansas City, Missouri in 1983; and did his residency in anesthesiology as well as fellowship in pediatric critical care/pediatric anesthesiology at Johns Hopkins Hospital during 1986-1989. He is board certified in pediatrics, anesthesiology, pediatric critical care and pain management,

Dr. Tobias has held various faculty positions of anesthesiology and pediatrics including Pediatric Pain, Pediatric Anesthesiology/ Pediatric Critical Care and Pediatric Cardiac Anesthesiology at the University of Missouri, University of Iowa and now The Ohio State University.

He has been associated with a number of professional societies and organizations; American Academy of Pediatrics, American Society of Anesthesiologists, International Anesthesia Research Society and Society of Critical Care Medicine just to mention a few.

Dr. Tobias has had a very distinguished professional and academic career and has won many awards and honors. Multiple Outstanding Achievement Awards in the School of Medicine, Teacher of the Year awards, Lifetime Achievement Award, International Biographical Centre of Cambridge, Quality Service Hero awards, and Best Doctors in America awards are just a few from a lengthy list of honors and awards bestowed upon him for his outstanding accomplishments.

He has served in various positions with editorial boards of many national and international medical journals and delivered hundreds of invited lectures. He extensively travelled to many of the developing countries in connection with Healing the Children and Heart Care International to provide anesthetic care for orthopedic, urology, and pediatric cardiac surgical missions.

Professor Tobias has authored hundreds of research articles, review articles, medical book chapters, web chapters, abstracts, letters to the editor and invited editorials etc. We are optimistic that his association with APICARE will prove fruitful for the further progress of the journal.

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