

Research Article

Comparative study of preoperative oral Pregabalin and oral Clonidine on postoperative analgesia

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Abstract: Background and Objectives: This is to study the efficacy of oral pregabalin and oral clonidine in preventing central pain sensitization and hence, effect on postoperative pain, when administered preoperatively as pre-emptive analgesics in various surgeries performed in our institution. **Materials and Methods:** 50 ASA I and II adult patients scheduled for elective surgeries were randomly divided into two groups. Group I received pregabalin 150 mg orally and Group II received clonidine 150 mcg orally, 60 minutes before surgery. Inj. Tramadol 1 mg/kg, as postoperative analgesic was given to both the groups intravenously tid. First dose was given immediately after shifting to postoperative ward. Inj. Diclofenac 1mg/kg i.m. was selected as rescue analgesic. Rescue analgesic was given if VAS score >4 and on patient demand. VAS was recorded in postoperative period and also total doses of rescue analgesics required in each group for 12 hours. Preoperative and postoperative vitals recorded and drug related side effects were also recorded. **Results:** Patients in group 1 had significantly lower VAS score, and required less rescue analgesic doses (3.08 ± 0.812 vs 4.12 ± 0.666) compared to group 2 in 12 hours. There were no demonstrable side effects related to pregabalin nor with clonidine. Hemodynamic parameters were comparable in both the groups except the MAP 0 and SBP 0 which were better in clonidine group. **Conclusion:** It can be concluded from our study that single dose preoperative pregabalin improves analgesia in early postoperative period and reduces analgesic consumption with a good safety profile compared to that of clonidine.

Keywords: Pain; postoperative; premedication; general anaesthesia.

INTRODUCTION

This decade has been designated as the decade of the pain control and research by the United States congress. Adequacy of perioperative pain control is one of the important factors in determining safe discharge from the surgical unit and has major influence on the patient's ability to resume normal daily activity. While there have been significant advancements in options for pain assessment and therapy, effective postoperative pain management remains frequent dilemma for patients and clinicians. Pain after surgery remains a significant clinical problem as it impairs recovery and may lead to chronic pain. Postoperative care involves pain management, prevention and treatment of postoperative complications, and recovery of preoperative function. Despite recent advances in physiology of acute pain over the past decades, approximately 80% of patients undergoing surgical procedure experiences postoperative pain¹. While postoperative pain at rest has been recognized to be

responsive to opioid therapy, attention has been shifted over the past two decades to the understanding and treatment of movement evoked or dynamic pain. Postoperative pain evoked by movement is considerably less responsive to Opioids. More importantly, poorly controlled movement evoked pain has been related to postoperative pulmonary, cardiac, and thromboembolic complications. These postoperative complications can be both devastating to the patient and costly to health care system.

The current concept of perioperative analgesia is mainly based on the combination of opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), small dose ketamine, and perioperative administration of local anesthetics. The use of opioids may be limited by adverse effects, such as nausea, vomiting, excessive sedation, pruritus, and urinary retention, the incidences of which have been reported to be 25%, 20%, 3%, 15%, and 23%, respectively.² NSAIDs are associated with

Quick Response Code



Journal homepage:

<http://www.easpublisher.com/easjacc/>

Article History

Received: 15.03.2019

Accepted: 01.04.2019

Published: 29.04.2019

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DOI: 10.36349/easjacc.2019.v01i02.002

damage to gastrointestinal mucosa, bleeding, renal toxicity, allergic reactions, and heart failure. Cyclooxygenase-2 selective NSAIDs may have pro-thrombotic properties, increasing the risk of stroke and myocardial ischemia.

Prevention and treatment of postoperative pain and complications such as nausea and vomiting, contributes to be a major challenge in postoperative care and plays an important role in the early mobilization and well-being of the surgical patient. Usage of adjuvants for perioperative pain control is well known. An ideal adjuvant drug for perioperative analgesia should have analgesic properties with opioid sparing effect and should not be associated with significant adverse effects. The testing of new analgesics as well as combinations of analgesics in order to reduce the need for opioids is the key area in acute pain research. Effective pain management improves pain satisfaction, decreases hospital stay and shortens recovery of the postsurgical patients. Anticonvulsant drugs could be useful in treating trigeminal neuralgia, epilepsy and neuropathic pain. Similarly, some parallels can be drawn between postsurgical and neuropathic pain. Although surgical nerve injury is indeed a cause of neuropathic pain, initiation mechanisms of postsurgical and neuropathic pain are usually different.

However, perpetuation and maintenance of neuropathic and postsurgical pain both often involve sensitization of primary afferent and second order dorsal horn neurons. Gabapentin and pregabalin are two mechanistically different types of analgesics that have demonstrated efficacy after a variety of surgical procedures. Anticonvulsant medications are established treatment for neuropathic pain. Pregabalin a structural analogue of gamma amino butyric acid (GABA) chemically described as 5- methyl-hexanoic acid, has been used for treatment of neuropathic pain, associated with diabetic peripheral neuropathy and post herpetic neuralgia. Pregabalin binds to alpha-2 delta subunit of presynaptic voltage gated dependent calcium channels in the tissues of central nervous system. The gabapentinoid group of drugs possesses excellent pain modifying properties along with sedation and anxiolysis. These characteristics make them an attractive choice for premedicating the patients. Clonidine hydrochloride is an imidazoline derivative with centrally acting alpha-2 adrenergic agonist activity. α 2-selective adrenergic agonists like clonidine has shown properties that are potentially beneficial for premedication to reduce sympathetic activity, the incidence of shivering and oxygen consumption during recovery from anesthesia, to decrease anesthetic and analgesic requirement and to minimize postoperative pain, nausea and vomiting. Clonidine provides significant benefits for preoperative anxiety and analgesia. Premedication with clonidine blunts the stress response to surgical stimuli and the narcotic and

anesthetic doses are also reduced.⁴⁸ Clonidine administration, in general Clonidine appears to decrease anesthetic and analgesic requirements (decrease MAC), provide sedation and anxiolysis. Pregabalin and clonidine has been proved to have similar pain modifying effect on neuronal structure and receptors in pain pathways. We feel that pregabalin and Clonidine may potentiate analgesic effects of other analgesics routinely used during general anaesthesia. The hypothesis of this study is to know the efficacy of pregabalin and clonidine as a premedicants in patients undergoing various surgeries under general anaesthesia.

MATERIALS AND METHODS:

SOURCE OF DATA

After Institutional Ethics committee's approval, fifty American Society of Anesthesiologists (ASA) physical status I-II adults scheduled for elective surgery under general anesthesia at A.J. Institute of Medical Sciences and Research Centre Hospital, Mangalore, between December 2014 and June 2016 were included in the study.

METHOD OF COLLECTION OF DATA

Fifty patients aged between 20 to 50 years posted for elective surgeries under general anaesthesia at A.J. Hospital, Mangalore were included in the study. After explaining the procedure, written informed consent was taken from all these admitted patients. The pre-anaesthetic evaluation was done and the patients were divided into two groups (Group I and Group II) of 25 each on the basis of random sampling method. This allocation to groups was done randomly, using randomisation through random number generator application method (Random number generator, Random # generator, application, Jess Tucker, version 1.1.3, 2013). The procedures which were included for patients of the study were commonly done general surgical, orthopaedic, and gynaecologic, otorhinolaryngeal and dental procedures.

Group I patients were made to take oral pregabalin 150 mg 1hr before surgery. Group II patients were made to take oral clonidine 150 mcg 1hr before surgery. Patients from both groups were kept nil per oral from solids for 8 hours and from clear fluids for 2 hours. All the patients were pre-medicated with injection glycopyrolate i.v. 0.005 mg/kg and injection fentanyl 1-2 μ g/kg before induction. Patients were monitored with ECG, noninvasive blood pressure and pulse oximetry (SpO₂). Baseline vitals were recorded and 18 Gauge i.v. cannula was secured, i.v. fluids (RL) were administered as 6-8ml/kg body weight. Pre-oxygenation with 8L/min of 100% O₂ via Mask, using Bains circuit was done for 3 minutes. A standard balanced general anesthesia technique was used in all patients. Induction was done with injection thiopentone sodium 5-7 mg/kg till loss of eyelash reflex. Endotracheal intubation was facilitated with injection succinylcholine 1.5 mg/kg i.v. Appropriate size cuffed

Endotracheal tube was inserted and the anesthesia was maintained with sevoflurane (1 MAC) with 66% N₂O & 33% O₂. Positive pressure ventilation was initiated with tidal volume and rate adjusted to maintain an end-tidal PCO₂ of 35–40 mm Hg. Neuromuscular blockade was maintained with vecuronium bromide based on neuromuscular monitoring. Intra-operative monitoring included ECG, NIBP, HR and SPO₂. At the end of surgery residual neuromuscular block was antagonized with injection glycopyrolate 0.01 mg/kg and neostigmine 0.05 mg/kg i.v. Extubation was performed after adequate recovery of muscle power and other extubation criteria were fulfilled.

After Tracheal extubation, patients were transferred to post-anesthesia care unit. Post-operative pain severity was assessed using VAS (scoring system of 0 -10, with no pain being 0 and most severe pain being 10). Assessment of VAS pain score were made at 0, 4, 8, 12 hours in post-operative period. Inj. diclofenac sodium 75 mg i.m. was given if VAS was three or more or on demand. Side effects were noted.

INCLUSION CRITERIA

- Patients aged between 20 to 50 years of age of both genders posted for elective surgeries under general anaesthesia.
- American Society of Anesthesiologists (ASA) grade I and II patients.

EXCLUSION CRITERIA

- Age less than 20 and more than 50 years.
- Patients belonging to ASA class III, IV and V.
- Pregnant females.
- Patients posted for emergency surgeries.
- Patients with body mass index more than 30kg/m².
- Patients with neurological, psychiatric or neurovascular disorder.

Parameters to be studied:

- Pain assessment score.
- Postoperative analgesic dose requirements.
- Preoperative and postoperative vitals and its significant deviations from the baseline.
- Adverse effects, if any.

RESULTS

a) The age and weight are compared between the groups using unpaired t test. There is no significant difference between pregabalin and clonidine group. The mean (SD) age was 35.68 (8.649) for group I, and 35.40 (9.544) for group II, ($P=0.8581$) analyzed by unpaired t test. The mean (SD) weight of group I was 54.24 (1.952) whereas group II was 51.44(1.716) with ($P=0.286$).

b) At each interval i.e. pre-operative HR (Baseline) and post-operative HR at 0, 4, 8 and 12 hr were compared between two groups and all values had $P > 0.05$, indicating that there was no significant difference in the heart rate between two groups.

c) From the baseline value, heart rates in pregabalin group reduced significantly at all intervals and P values at all the intervals were found to be highly significant with P value <0.005 .

d) There were statistically significant changes in heart rate at 4 hr and 8 hr from baseline in Clonidine group.

e) MAP values were not statistically significant between two groups, except at 0 hr where it is significantly decreased in Clonidine group.

f) The MAP values reduced significantly at all intervals and P values at 0 hr interval was found to be highly significant with P value <0.005 in Clonidine group when intragroup comparison was done. There were no variations seen in Pregabalin group.

g) SBP in both the groups were compared at baseline and at various intervals. It was associated with significant difference between two groups at 0 hr and 4 hr. DBP in both groups were comparable.

h) When compared to clonidine group, VAS scores of pregabalin group showed lower values. Though significant lower VAS scores were noted in pregabalin group at all intervals, it was highly significant at baseline with $P<0.001$ and moderately significant at 8 and 12th hours with $P<0.01$.

i) Mean doses required in clonidine group were 4.12 (0.66) as compared to pregabalin group where total number of rescue doses were 3.08 (0.81) which was highly significant. Out of 25 patients in each group, clonidine group had 24 patients [96 % of the group] who required rescue analgesic doses whereas in pregabalin group, it was 16 patients [64 % of the group] with P value of 0.0133 which is statistically significant.

j) Out of 25 patients in each group, 4 patients in clonidine group had drowsiness [16 %] and 4 patients had dry mouth [16%] whereas, in pregabalin group, 2 patients had drowsiness [8 %] and 1 patient had dry mouth [4 %].

Figures

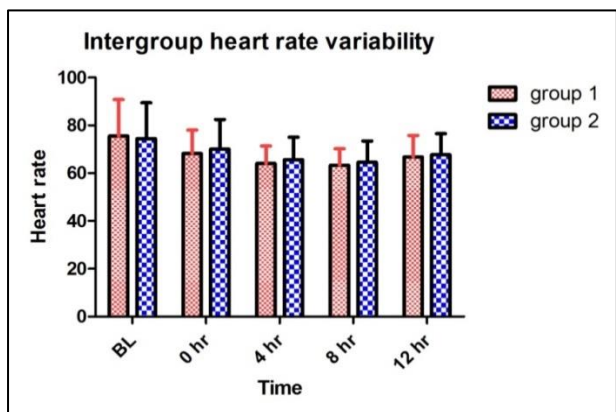
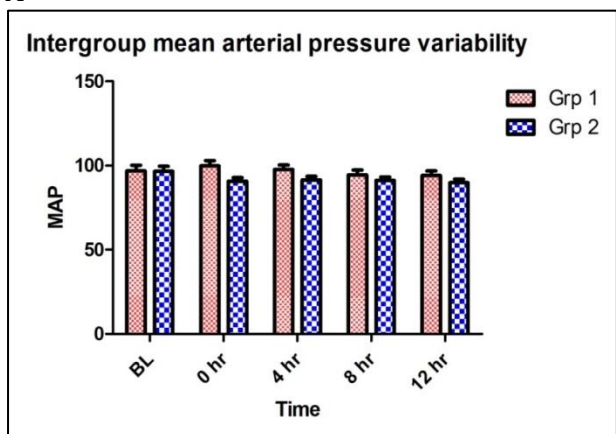


Figure Legend 1: Heart rate variability comparison between Pregabalin and Clonidine group. There was no significant difference in the heart rate between two groups.

A



B

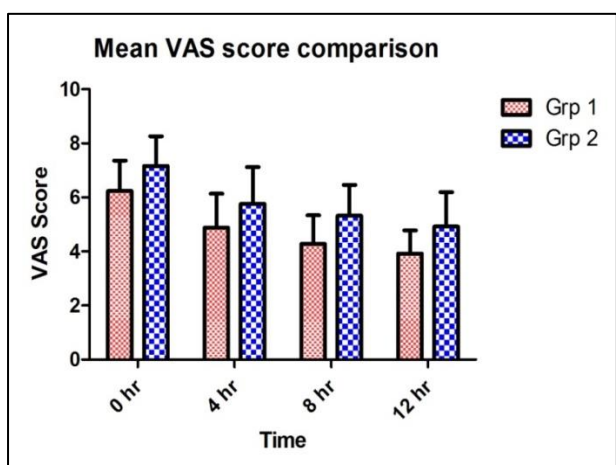


Figure Legend 2: (A) –MAP comparison between two groups. MAP values were not statistically significant between two groups

(B) – VAS score comparison between two groups. Though significant lower VAS scores were noted in pregabalin group at all intervals, it was highly significant at baseline and moderately significant at 8 and 12th hours.

Tables

Table 1: Heart rate comparison between two groups. The values are represented as mean and standard deviation. The units are in beats per minute. Heart rates in both the groups were compared using unpaired t test

HR	Pregabalin	Clonidine	P value	t	summary
Baseline	75.52 ±15.3	74.44 ±15.05	0.802	0.252	NS
0 hr	68.20 ± 9.85	70.08 ± 12.40	0.556	-0.593	NS
4 hr	64.08 ± 7.29	65.64 ± 9.43	0.516	-0.654	NS
8 hr	63.28 ± 6.96	64.56 ± 8.88	0.573	-0.567	NS
12 hr	66.76 ± 9.07	67.72 ± 8.86	0.707	-0.378	NS

Abbreviations: hr : Hour; NS: nothing significant; t: t value in T test

Table 2: Intra group heart rate variability in Clonidine group tested using ANOVA test. The values are represented as mean difference and standard deviation. The units are in beats per minute. There was no significant change from baseline to 0 hr HR. However, there were statistically significant change in heart rate at 4 hr and 8 hr from baseline.

Clonidine HR bonferroni's multiple comparisons test	Mean Diff.	SD	Significant? P < 0.05?	Summary
baseline vs. 0 hr	4.362	12.75	No (0.1)	NS
baseline vs. 4 hr	8.800	10.38	Yes (0.00)	**
baseline vs. 8 hr	9.800	12.67	Yes (0.001)	***
baseline vs. 12 hr	6.720	12.52	Yes (0.013)	*

Abbreviations: hr : Hour; HR: Heart Rate; NS: nothing significant

Table 3. Intergroup variability of MAP at various time intervals. The values are represented as mean and standard deviation. The units are in mm Hg. MAP compared between two groups using unpaired t test and P values were noted. MAP values were not statistically significant between two groups, except at 0 hr where it is significantly decreased.

MAP	baseline	0 hr	4 hr	8 hr	12 hr
Pregabalin	96.80 ± 3.338	99.80 ± 3.082	97.64 ± 2.66	94.48 ± 2.820	94.00 ± 2.828
Clonidine	96.61 ± 2.917	90.67 ± 2.167	91.49 ± 2.045	91.17 ± 2.063	89.76 ± 2.121
Pvalue	0.967	0.019	0.073	0.349	0.236
t	0.042	2.424	1.831	0.946	1.199
Summary	NS	*	NS	NS	NS

Abbreviations : hr: hour; t: t value in T test

Table 4. VAS score comparison between two groups. Mean of VAS scores at 0 (baseline), 4th, 8th and 12th postoperative hour between the Pregabalin and Clonidine groups were compared using unpaired t test. When compared to clonidine group, VAS scores of pregabalin group showed lower values. Though significant lower VAS scores were noted in pregabalin group at all intervals, it was highly significant at baseline with P<0.001 and moderately significant at 8 and 12th hours with P<0.01.

VAS	Pregabalin Mean ±SD	Clonidine Mean±SD	P value	C.I.	t	Summary
VAS 0	6.24±1.12	7.16±1.10	0.0054	0.28 to 1.55	2.911	***
VAS 4	4.88±1.26	5.76±1.36	0.022	0.13 to 1.63	2.36	*
VAS 8	4.28±1.06	5.32±1.14	0.001	0.41 to 1.66	3.33	**
VAS 12	3.92±0.86	4.92±1.28	0.002	0.37 to 1.62	3.23	**

Abbreviations :VAS : Visula analogue scale; C.I.: Confidence interval; t : t value in T test

DISCUSSION

Effective postoperative analgesia is necessary to provide subjective comfort and alleviate the suffering in patients undergoing surgery. Surgical stimulation or mechanical hyperalgesia in postoperative wounds appear to share a common mechanism with heat induced experimental secondary hyperalgesia which leads to sensitization of dorsal horn neurons and subsequently to central neuronal sensitization which are associated with augmentation of postoperative pain. Postoperative pain is typically regarded as a type of pain with peripheral mechanoreceptors stimulation involving inflammatory neurogenic and visceral mechanism, with a transient, reversible type of neuropathic pain. The invention of newer generation of potent and safe pharmacological agents has opened up a lot of options and multimodal approach for providing adequate pain relief in post-surgical patients. The choice of such an agent is guided by factors such as efficacy, convenience of administration, cost-effectiveness, safety profile and additional advantage associated with the outcome variable relative to a standard analgesic regimen. The aim of combining different analgesic drugs is to obtain synergistic or additive analgesia, allowing a smaller dose of each drug with an improved safety profile. This can be achieved by combining analgesics with different mechanism of actions.

In recent years, pregabalin has been introduced as an adjunct in the multimodal management of postoperative analgesia. Anti-hyperalgesia drug such as pregabalin has some proven role in the control of postoperative pain either singly or in combination with other anti-nociceptive drug for synergistic effects; and various clinical studies with the drugs for postoperative analgesia have shown promising results. It acts by limiting the short-duration wind-up component of central sensitization by binding to the pre-synaptic alpha-2-delta subunit of voltage gated calcium channels which are distributed widely in the spinal cord and brain. The conformational changes induced by this binding inhibit abnormally intense neuronal activity by reducing the synaptic release of glutamate and other neurotransmitter. Experimental studies with animal models and healthy volunteers have shown that pregabalin reduces nociceptive responses, particularly in condition involving central sensitization.

The α2-agonist clonidine has shown properties that are potentially beneficial for premedication to reduce sympathetic activity, the incidence of shivering and oxygen consumption during recovery from anesthesia, to decrease anesthetic and analgesic requirement and to minimize postoperative pain, nausea and vomiting. Clonidine provides significant benefits for preoperative anxiety and analgesia. Premedication with clonidine blunts the stress response to surgical stimuli and the narcotic and anesthetic doses are also reduced.48 Clonidine administration, in general appears

to decrease anesthetic and analgesic requirements (decrease MAC), provide sedation and anxiolysis.

In our study, we have compared the effect of preoperative oral pregabalin and oral clonidine on postoperative analgesia in patients undergoing general anaesthesia. Group I patients received oral pregabalin 100mg 1 hour prior to the surgery and the Group II patients received oral clonidine 100mcg 1 hour prior to the surgery. Baseline and postoperative vitals, VAS scores, number of rescue analgesics required were assessed in all the patients. VAS scores were the primary outcome variables to measure the quality of analgesia. Being aware that VAS scores have subjective variations, the other outcome variables like the total number of patients requiring rescue analgesic and the total dose required were also recorded and compared between 2 groups. In this prospective randomized study, we found that the postoperative pain VAS scores were significantly reduced at different interval assessments compared to the clonidine group.

Extensive review of literature on pregabalin with respect to the dose used revealed the use of different doses ranging from 50 to 600 mg with varied efficacy. In a randomized controlled trial by Paech *et al.*, 100 mg preoperative pregabalin was used to compare the postoperative pain relief after minor gynecological surgery. Their primary outcome was pain score in the recovery unit and patients were followed for 24 h. They have found no significant difference between groups for pain experienced in the recovery room nor for the recovery room fentanyl requirement among the two groups. This result might be due to the dose they have used in their study. We have used a higher dose, 150 mg, in our study and it has shown a significant difference in postoperative pain VAS scores and the postoperative analgesic requirement between the groups. In contrast to their results of higher incidence of side effects of pregabalin like light-headedness, visual disturbance, and difficulty with walking, we haven't found any significant adverse effects in our patients. This could be due to the different type of study population and the type of surgery.

Hill *et al.*, found no difference between pregabalin 50 mg and placebo, but a statistically significant reduction in pain and pain intensity difference after 300 mg.

Reuben *et al.*, 140 also used a larger dose of 150 mg, given on two separate occasions, and found it to be an effective treatment for reducing pain both at rest and with movement over the 24-h postoperative time period. Agrawal *et al.*, gave patients a 150 mg dose of pregabalin, before a laparoscopic cholecystectomy under general anesthesia to relieve pain. The pain intensity and fentanyl consumption was significantly lower in the group receiving pregabalin, than in the control group.

CONCLUSION

Our clinical study demonstrated that preoperative oral pregabalin reduces diclofenac requirement post-operatively which was significantly lower as compared to clonidine group. It has a definitive role in reducing postoperative pain and analgesic requirement in patients undergoing various surgeries under GA. At a dose of 150mg, it was devoid of any adverse effects and hemodynamic changes. So, it can be concluded from our study that single dose preoperative pregabalin 150mg 1hour before surgery improves analgesia in early postoperative period and reduces analgesic consumption without any statistically significant side effects when compared to preoperative clonidine 150mcg 1 hour before surgery.

Acknowledgements

Firstly, I would like to express deepest gratitude to my guide Dr. Gururaj Tanthry, Associate Professor, Department of Anaesthesiology, A.J. Institute of Medical Sciences, Mangalore for his full support, expert guidance, understanding and encouragement throughout my study and research. Without his incredible patience and timely wisdom and counsel, my thesis work would have been an overwhelming pursuit.

I owe my gratitude to Dr. Karunakara K Adappa, Professor and Head of the Department of Anaesthesiology, A.J. Institute of Medical Sciences, Mangalore for his guidance and timely support. I would like to thank Dr. Thrivikrama Padur Tantry, Professor, Department of Anaesthesiology, A.J. Institute of Medical Sciences, Mangalore for his infectious enthusiasm and unlimited zeal in helping me with my thesis. I offer my sincere appreciation to Dr. Gurudutt Rao, Dr. Keshav Rao for their thought provoking ideas and co-operation during my postgraduate course. My heartfelt thanks to Dr. Harish Karanth, Dr. Vasanth Shetty, Dr. Vijesh, Dr. Pramal Shetty, Dr. Chethan, Dr. Rithesh Shetty, Dr. Murali Shankar, Dr. Reshma, Dr. Abhin and Dr. Preetham for their unconditional help, moral support and guidance during the preparation of this dissertation. I am grateful to Dr. Ashok Hegde, Dean, for extending his help towards the completion of this dissertation.

Conflict of Interest

There are no conflicts of interests.

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