

# Effect of indian classical music (raga therapy) on fentanyl, vecuronium, propofol requirements and cortisol levels in cardiopulmonary bypass

## Abstract

**Background:** This study was carried out to evaluate the effect of Indian Classical Music (Raga Therapy) on Fentanyl, Vecuronium, Propofol requirements and cortisol levels during cardiopulmonary bypass. Cardiopulmonary bypass is associated with immense stress response and high levels of intra operative cortisol levels which is detrimental to the patient and involves large doses of Fentanyl, Propofol and Vecuronium requirement to maintain hemodynamic stability intra operatively. We evaluated the effect of Indian classical music therapy on cortisol levels and the above drugs requirement during cardio pulmonary bypass.

**Methods:** After obtaining clearance from Institutional Ethical Committee and written informed consent from patients, 34 patients were assigned to either Group M Music group (n=17) and Blank CD Group C (n=17). The patient's awareness level and depth of anesthesia was monitored by BIS (Bi spectral index), Fentanyl and Propofol infusion titrated to a BIS score of 50 and neuromuscular monitoring was done by Post tetanic count (PTC) in the Adductor Pollicis muscle. Vecuronium was repeated whenever a PTC count of 7 was achieved, in both the groups. Music therapy or blank CD was played by earphone, in the patient's ear in both the groups, from 30minutes before induction to till the patient was shifted to the ICU.

**Result:** The authors found significant decrease in the cortisol levels both after sternotomy and after aortic cross clamp release. In the Music group (Group M) which was 30% less than Blank CD group (Group C). Fentanyl, Propofol and Vecuronium requirement in the Music group were reduced by 30% and 25% and 25% respectively, which were statistically significant ( $P < 0.05$ ).

**Conclusion:** Intra operative Indian classical music therapy effectively reduced the intra operative stress (as revealed by reduced levels of cortisol) and reduced the requirement drugs (Fentanyl, Propofol and Vecuronium) during Cardiopulmonary bypass.

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## Introduction

"Music is the medicine of the future," said Edgar Cayce in 1947 and who healed thousands of people while in a Trance State. There is documentary evidence that shows the power of music can be tapped to heal the body, strengthen the mind and unlock the creative spirit. Published papers and journal articles offer dramatic accounts of how doctors, musicians, and healthcare professionals use music to deal with everything from anxiety<sup>1-4</sup> to cancer,<sup>5-7</sup> coronary artery disease,<sup>8-11</sup> chronic pain,<sup>12-14</sup> and mental illness<sup>14-16</sup> even in Alzheimer's disease.<sup>17</sup> During childbirth, music can relieve expectant mothers' pain and anxiety and help release endorphins, the body's natural painkillers, dramatically decreasing the need for sedation and analgesia.<sup>18,19</sup> Exposure to sound, music and other acoustical vibrations can have a lifelong effect on health, learning, and behaviour. Regular music therapy can improve emotional communication and interaction between parent and child.<sup>16</sup> Music has been used as a treatment or cure from migraines<sup>20</sup> to substance abuse.<sup>21</sup>

Cardiopulmonary bypass is associated with immense stress response which is reflected by increased cortisol levels even after maintenance of deep anaesthesia. Standard intra operative management protocol includes use of an opioid based analgesic (e.g., Fentanyl), sedatives (e.g., Propofol, midazolam) and muscle relaxant (e.g., Vecuronium) in high dose to maintain adequate anesthesia level. An increased cortisol level brings in its array of many systemic complications including hyperglycaemia. The aim of the study was to

evaluate the effect of Indian classical music therapy on cortisol levels and the above drugs requirement during cardio pulmonary bypass.

## Materials and methods

After obtaining Institutional Ethics Committee approval and informed written consent, thirty four patients 18 to 65 years of age posted for elective cardiac surgery under cardiopulmonary bypass were included in this randomized double blinded placebo controlled study. Patients with pregnancy, uncontrolled heart failure, concomitant systemic illness, pre-existing adreno cortical disease, deafness, uncontrolled psychosis and schizophrenics who become violent on listening to music, those having contraindication to general anesthesia protocol and patients who refused to participate in the study were excluded. The patients were randomly divided into two groups: group M and group C by a computer-generated randomization chart. Group M (Music group) received Raga therapy in the form of Raga DARBARI played through a CD player with the output in the earphone connected to the patient's ears from 30mins before induction to throughout the operative procedure (till the patient was shifted to the ICU). Group C (Blank CD group) patients had earphones placed in their ears in a similar manner except that blank CD was played throughout the procedure. Data was collected by an anaesthesiology resident blinded to the study. Once the patients were wheeled inside the operation theatre, SpO<sub>2</sub> probe, 5 lead E.C.G, and BIS electrodes were attached and monitoring was done. Then under local anaesthesia I.V line was inserted in the right dorsum and arterial line was inserted

in the left radial artery and arterial blood pressure monitoring was done. Induction of anaesthesia was done with incremental doses of Fentanyl 2 to 5µg/kg till BIS score of 50 was reached with due consideration to stable patient hemo dynamics. Then sleep dose of thiopentone sodium was administered. Intubation of the trachea was done with the help of Rocuronium 1.2mg/kg. Then central venous line was inserted in the right internal jugular vein. Maintenance of anaesthesia was done with nitrous oxide in oxygen (till the onset of CPB), inj Fentanyl, midazolam, and isoflurane (0.6 to 1 percent by volume) titrated to the BIS score of 50. Neuromuscular monitoring was done in Adductor Pollicis muscle supplied by the ulnar nerve with post tetanic count (PTC) and Vecuronium 2mg was repeated at post tetanic count of seven. All the patients received heparin 4 mg/kg with the aim of maintaining activated clotting time (ACT) > 480 seconds. After onset of CPB and cross clamping of aorta, ventilation in both the groups was discontinued. In both the groups normal ventilation was restored after release of aortic cross clamp. After the patient weaned off CPB, residual action of heparin was reversed by administration of protamine sulfate (1:1.3:heparin:protamine) intravenously. After the surgical closure was accomplished the patients were shifted to ICU. Comparison of the serum cortisol levels in both the groups both preoperatively and after release of aortic cross clamp was done. Comparison of the intra operative Fentanyl, Propofol and Vecuronium and midazolam requirement in both the groups in maintaining a BIS score of 50 was done.

## Statistics

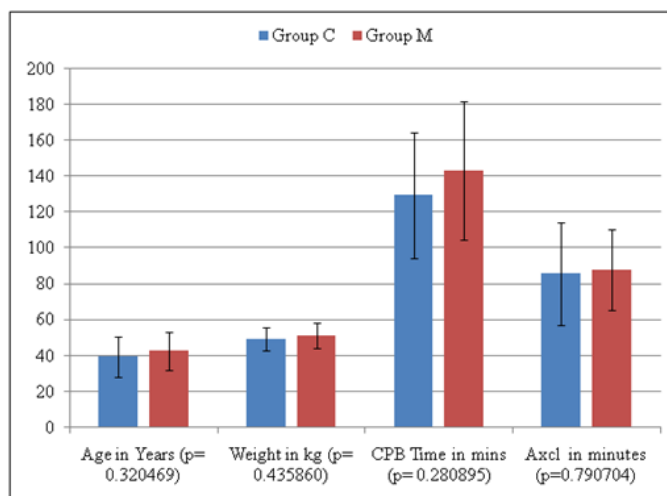
For sample size calculation the study parameters namely serum cortisol and requirement of intra operative fentanyl, vecuronium and propofol were considered. Study values were obtained from previous studies. Our study has 80% power and 5% probability of type I error for all study variables. For cortisol level, it was estimated that 17 subjects would be required per group in order to detect a 25 % reduction in cortisol level between controls and test groups (from 200mmol/L to 150mmol/L) assuming a standard deviation of 50mmol/L. For intra operative fentanyl requirement, assuming standard deviation of 50µg, 10% reduction between control and test groups (800µg-720µg) was considered significant and required sample size was calculated to be 8 subjects per group. For intra operative vecuronium requirement, 20% difference between control and test groups (30mg-24mg) was considered significant and required sample size was 12 subjects per group. Considering 20% reduction in total propofol requirement between control and test group (300mg-240mg) assuming standard deviation of 50mg in total intra operative propofol requirement, it was calculated that 12 subjects would be required per group in order to detect such a difference. Therefore 34 subjects, equally distributed between the two groups were kept as the recruitment target.

All raw data were entered into a Microsoft excel spread sheet and analysed using standard statistical software statistical version 6 Stat Soft Corporation Tulsa Oklahoma. Randomization was done using computerised random number list. Numerical variables were compared between groups by Student's independent sample t test if normally distributed or Mann- Whitney U test if otherwise. Chi square test or fisher's exact test was employed for inter-group comparison of categorical variables. Two tailed P value < 0.05 was considered as statistically significant.

## Results

All the thirty-four patients (group M; n=17 and group C n=17) enrolled, completed the study and underwent intra operative and

24hours of inpatient monitoring .There was no significant difference in the patient characteristics ,demographic profile, CPB time and aortic cross clamp time between the two groups (Figure 1).



**Figure 1** Comparison of the patient characteristics, demographic profile, CPB time and aortic cross clamp time.

Comparison of the intra-operative parameters between the two groups shows statistically significant reduced mean intra-operative requirement of fentanyl, propofol, Vecuronium and reduced but not statistically significant requirement of midazolam in group M (Table 1). Serum cortisol level at 30minutes after induction and after removal of aortic cross clamp was significantly higher in group C. Capillary blood glucose level measured at the same time were compared and revealed significantly high values in group C.

## Discussion

Music is the gift of god to mankind. It is a drug without any side effects. Indian classical music is highly evolved through many generations and Ragas have been claimed to have therapeutic values. In this study Indian classical music (Raga Therapy) with raga Darbari (originally composed by Tansen in the court of the great Mughal emperor Akbar) reduced intra operative stress and cortisol levels. The physiological basis of the beneficial effects of the soothing and comfortable sound of music may be appreciated from some clinical studies and anecdotal evidence. Dopaminergic pathways and central opioid regulatory pathways have been implicated in several studies.<sup>22-26</sup> Positron emission tomography (PET) scan<sup>22-23</sup> as well as functional magnetic resonance imaging (fMRI) of human brain<sup>24-26</sup> has revealed that pleasurable and chill inducing music can increase regional cerebral blood flow to the mesocorticolimbic system including ventral striatum [including the nucleus accumbens (NAc)] and midbrain, as well as the thalamus, cerebellum, insula, anterior cingulate cortex (ACC) and orbito frontal cortex (OFC) which are critical to reward and reinforcement as well as strong deactivations in the amygdala, hippocampus, para hippo campalgyrus, and the temporal poles.<sup>25</sup> Musical reward also involves activation of as opioid-rich midbrain nuclei known to regulate morphine analgesia and descending inhibition of pain.<sup>24</sup> Listening to music also have effect on the regulation of the hypothalamic-pituitary axis, the sympathetic nervous system, and the immune system, which have key functions in the regulation of metabolism and energy balance.<sup>27,28</sup> Another attractive hypothesis is music therapy interferes with dopaminergic neurotransmission and increase growth hormone production and thus reduces IL-6 production from leucocytes.<sup>28</sup>

Communication with the external environment while the patient is under general anaesthesia has long been a debated topic. Consciousness during anaesthesia is a well recognized possibility and it affects 0.1 to 5% of patients.<sup>29</sup> Effect of music therapy in unconscious patients has been described in different studies.<sup>30-32</sup>

### Raga chikitsa: the indian music therapy

Raga, we all know is the sequence of selected notes (swaras) that lend appropriate 'mood' or emotion in a selective combination. Depending on their nature, a raga could induce or intensify joy or sorrow, violence or peace and it is this quality which forms the basis for musical application. Thus, a whole range of emotions and their nuances could be captured and communicated within certain rhythms and melodies. Playing, performing and even listening to appropriate ragas can work as a medicine.<sup>33</sup> Various ragas have since been recognized to have definite impact on certain ailments. Some ragas like Darbari Kanhada, Kamaj and Pooriya are said to help in defusing mental tension, and reduce the intensity of pain felt by the subjects. For those who suffer from hypertension, ragas such as Ahir bhairav, Pooriya and Todi are prescribed.<sup>34,35</sup> To control anger and bring down the violence within, carnatic ragas like Punnagavarali, Sahana etc. do come handy. It is generally believed in music circles, though scientific endorsement doesn't appear to be forthcoming.<sup>36</sup>

The stress response to surgery has some definite neuro chemical basis.<sup>37</sup> Surgical stress gives rise to activation of sympathetic nervous system as well as hypothalamus-pituitary axis and involves increased secretion of TNF- $\alpha$ , IL-1, IL-6, ACTH, arginine vasopressin (AVP, antidiuretic hormone [ADH]), prolactin and multiple other mediators which ultimately gives rise to increased serum cortisol, blood glucose and other inflammatory mediators and responsible for acute and chronic ill health. Cardiac surgery is accompanied by tremendous increase in cortisol level especially at the time of aortic cross clamp release. Increased cortisol levels bring in its array myriad complications like hyperglycemia, increased blood pressure, increased fluid retention and pulmonary edema.<sup>38</sup>

The mean cortisol level in Mmol/L 30 minutes after induction and after aortic cross clamping were significantly less in group M ( $127.778 \pm 31.82$  &  $264.588 \pm 53.78$  Mmol/L) in comparison to group C ( $211.99 \pm 39.01$  &  $528.111 \pm 149.48$  Mmol/L) ( $p < 0.05$ ) (Figure 2) as is revealed by decreased requirement of anaesthetics. Reduction in fentanyl requirement was statistically significant ( $817.82 \pm 46.57$  micrograms in group M in comparison to  $994.117 \pm 24.25$  in group C in micrograms). ( $p < 0.05$ ) (Table 1). The intra operative mean Propofol requirement in milliliters (each milliliter containing 10 mg of Propofol) was significantly less in Group M ( $22.94 \pm 2.53$  ml) in comparison to group C ( $31.76 \pm 5.847$  ml). ( $p < 0.05$ ). The mean intra operative midazolam requirement in milligram in group M ( $5.23 \pm 0.43$  mg) though less than group C ( $5.58 \pm 0.50$  mg), but was not statistically significant ( $p > 0.05$ ). The requirement of muscle relaxant Vecuronium in milligrams was significantly less in group M ( $8.35 \pm 0.78$  mg) in comparison to group C ( $10.23 \pm 0.66$  mg) ( $p < 0.05$ ) (Table 1). Capillary blood glucose level was also significantly lower in group M (Figure 3).

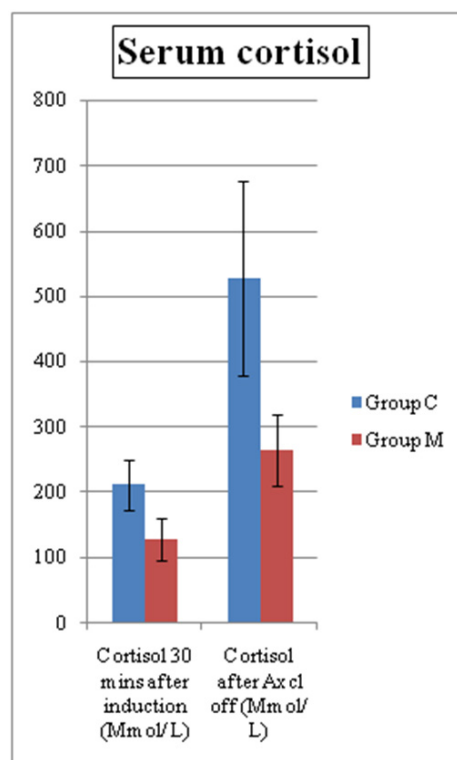


Figure 2 Comparison of serum cortisol level.

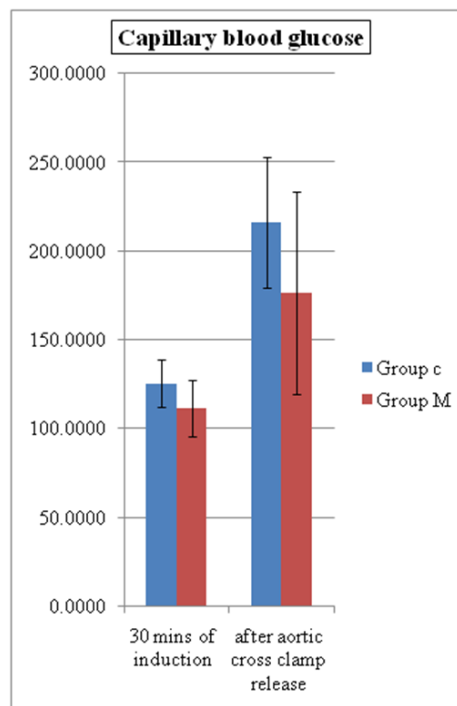


Figure 3 Comparison of Capillary blood glucose level.

This study is the only of its kind in the whole world that has employed a system of music to reduce intraoperative stress of cardiopulmonary bypass, though other form of music may be equally effective depending upon the prevalent culture. The molecular mechanism how music actually reduces stress is yet to be elucidated and further research in this regard need to be conducted. Studies on music therapy in cardiac patients yielded contradicting results.

	P value
Cortisol 30 mins after induction (Mmol/ L)	0.000000
Cortisol after Axcl off (Mmol/ L)	0.000000

	P value
30 mins of induction	0.008614
after aortic cross clamp release	0.022020

Bradt J et al.,<sup>8</sup> in a Cochrane database systematic review examined the effects of music interventions with standard care versus standard care alone on psychological and physiological responses in coronary heart disease patients. Their research revealed listening to music may have a beneficial effect on anxiety in persons with CHD, especially those with a myocardial infarction. They found beneficial effect of music on systolic blood pressure, heart rate, respiratory rate, quality of sleep and pain in persons with CHD. They opined in favour of music of patient's choice. Although in their view the clinical significance of these findings was unclear.

White JM<sup>11</sup> compared the effect of quiet restful environment and that with music in 45 patients with acute myocardial infarction and found reduction in heart rate, respiratory rate and myocardial oxygen demand. Whereas, very recently, Ripley L et al.,<sup>39</sup> examined determine the impact of music intervention on endothelial function, hemodynamics, and patient anxiety before, during, and after cardiac catheterization in the FEAT study. They found no vasodilator response, no lowering of blood pressure or heart rate, and no benefit from anxiety or stress discomfort in patients who underwent coronary angiography. Although the author's study was conducted on a different subset of patients, the probable benefit on cardiac patients as revealed in Cochrane database review supports the findings.

## Conclusion

In conclusion it can be said the effect of Indian Classical Music Therapy (Raga Therapy) on cortisol levels during CPB and its impact on analgesic requirement are dramatic. Music is a drug without any side effects. Further research need to be conducted taking into consideration the impact on music on other stress parameters, the selective effect of different Ragas on different organ systems and other markers of inflammation during cardiopulmonary bypass.

The limitations of this study include a failure to assess the catecholamine level as a marker of stress response and failure to extend

the music therapy into the postoperative period. A further study needs to be undertaken taking all these limitations into considerations to prove the claim of authors about the effectiveness of Indian classical as a stress reducer in cardiopulmonary bypass.

## Acknowledgments

None.

## Conflicts of interest

Author declares there are no conflicts of interest.

## References

1. Domi R, Laho H. Anesthetic challenges in the obese patient. *J Anesth.* 2012;26(5):758-765.
2. Huschak G, Busch T, Kaisers UX. Obesity in anesthesia and intensive care. *Best Pract Res Clin Endocrinol Metab.* 2013;27(2):247-260.
3. Kohn RM. Breath-holding test for cardiac states. *Circulation.* 1959;20:721-722.
4. Snider TH, Stevens JP, Wilner FM, et al. Simple bedside test of respiratory function. *JAMA.* 1959;170(14):1631-1632.
5. Greene BA, Berkowitz S. Preanesthetic induced cough as a method of diagnosis of preoperative bronchitis. *Ann Intern Med.* 1959;37(4):723-732.
6. Ard RW, Twining RH. Evaluation of valsalva test in bedside diagnosis of dyspnea. *Am J Med Sci.* 1957;234(4):403-412.
7. Ciftci F, Sen E, Akkoca Yıldız O, et al. A comparison of cardiopulmonary exercise test and 6 minute walking test in determination of exercise capacity in chronic obstructive pulmonary disease. *Tuberk Toraks.* 2014;62(4):259-266.