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Comparison of efficacy between intravenous clonidine and dexmedetomidine as pre-medication in attenuating hemodynamic stress responses during laparoscopic cholecystectomy

Diptimay Majumder[1], Susanta Kumar Halder[2], Swarup Datta[3], Sruthi Naresh[4], Soma Chakraborty[5], Subrata Pahari[6]

[1]Post Doctoral Trainee, Department of Cardiac Anesthesia, R.G. Kar Medical College, Kolkata, [2]Associate Professor, Department of Anesthesiology, Deben Mahato Government Medical College and Hospital, Purulia, [3]Associate Professor, Department of Anesthesiology, Bankura Sammilani Medical College, Bankura, [4]Post Doctoral Fellow, Department of Onco-Anesthesia, Tata Medical Centre, Kolkata, [5]Associate Professor, [6]Professor, Department of Anesthesiology, IPGME and R, Kolkata, West Bengal, India

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ABSTRACT

Background: Laparoscopic cholecystectomy is a commonly performed surgery and stable intraoperative hemodynamic status is desirable during pneumoperitonium. Clonidine and dexmedetomidine (alpha-2 adrenergic agonist) were used in this study to attenuate the stress response of pneumoperitoneum because alpha-2 adrenergic agonists help in the attenuation of neuroendocrine and hemodynamic responses to surgery and anesthesia, due to its sympatholytic action. **Aims and Objectives:** The aims and objectives of the study are to conduct a comparative evaluation of clonidine and dexmedetomidine as pre-anesthetic medication for the attenuation of hemodynamic changes during laparoscopic cholecystectomy surgeries. **Materials and Methods:** Eighty patients of either sex, aged 20–50 years, complying to the American Society of Anesthesiologists physical status I-II, scheduled for elective laparoscopic cholecystectomy under general anesthesia were divided into two equal groups to receive either clonidine 1 mg/kg (Group-C, n = 40) or dexmedetomidine 1 mg/kg (Group-D, n = 40), both injected through intravenous route as 15 mL volume with normal saline. Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and SpO_2 were measured before and after giving the study drugs, before and immediately after pneumoperitoneum, and then, at 10, 20, 30, 40, and 50 min of pneumoperitoneum. **Results:** Statistically significant difference was observed in heart rate in the dexmedetomidine group constantly since giving study drug, immediately after the creation of pneumoperitoneum, and then, 10, 20, 30, 40, and 50 min after pneumoperitoneum. Systolic, diastolic, and mean blood pressures were found to be significantly lower in Group D (except after administering study drug), immediately after creating pneumoperitoneum, and 10, 20, 30, 40, and 50 min after pneumoperitoneum. **Conclusion:** Dexmedetomidine as pre-medication is more efficacious in attenuating hemodynamic stress responses in laparoscopic cholecystectomy surgeries compared to clonidine as pre-medication.

Key words: Clonidine; Dexmedetomidine; Laparoscopic cholecystectomy; Stress response; Pneumoperitoneum

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Address for Correspondence:
Dr. Soma Chakraborty, Associate Professor, Department of Anesthesiology, IPGME and R, Kolkata-20, West Bengal, India.
Mobile: +91-9547032006. **E-mail:** drsoma.chakraborty@gmail.com

INTRODUCTION

Nowadays, laparoscopic cholecystectomy has become the gold standard for the treatment of cholelithiasis.[1] This modern surgical technique involves insufflation of gas (usually CO_2) into the peritoneal cavity, under pressure. This pneumoperitoneum raises the intra-abdominal pressure which in turn leads to increased plasma renin activity, raised plasma catecholamine levels, and increased circulating blood volume.[1] Anesthesiologists often face challenges to manage such hemodynamic changes.[2]

It has been reported in studies that there is a 10–30% reduction in cardiac output during pneumoperitoneum.[3] Increases in arterial pressure can pose a risk for adverse cardiovascular events in patients with pre-existing essential hypertension, ischemic heart disease, or increased intracranial pressure.[4] Hypercapnia and pneumoperitoneum stimulate sympathetic nervous system, causing catecholamine and vasopressin release.[5]

Various measures have been used to attenuate these hemodynamic responses such as deepening level of anesthesia with higher concentration of inhalational and intravenous anesthetic agents, high dose of opioids, antihypertensives such as beta-adrenergic blockers, sodium nitroprusside, regional or local neural blockade with local anesthetics.

Clonidine, with elimination half-life of 6–10 h, is a centrally acting selective partial α-2 agonist (220:1, α-2 to α-1). It is known to induce sedation and improve perioperative hemodynamic by attenuating blood pressure and heart rate responses to surgical stimulation. Clonidine is known to protect against perioperative myocardial ischemia. It provides sympathoadrenal stability and suppresses renin-angiotensin activity.[2] In addition, clonidine increases cardiac baroreceptor reflex sensitivity to increase in systolic blood pressure and thus stabilizes blood pressure.[6]

Dexmedetomidine, with elimination half-life of 2–3 h, is a highly selective and potent α-2 agonist (1620:1, α-2 to α-1) and is 7–10 times more selective for α-2 receptors compared to clonidine and has a shorter duration of action.[7] Dexmedetomidine is considered full agonist at α-2 receptors as compared to clonidine, which is considered a partial agonist.

Laparoscopic cholecystectomy is a commonly performed surgery and it is desirable to have a stable intraoperative hemodynamic status. Hence, this study was designed to observe the effect of dexmedetomidine and clonidine which is an established antihypertensive, in attenuating intraoperative hemodynamic stress responses to pneumoperitoneum, when both drugs are administered intravenously as pre-anesthetic medication.

Aims and objectives

The study was aimed at comparing the effect of pre-medication with dexmedetomidine or clonidine on mean arterial pressure (MAP) at 10 min after pneumoperitoneum in patients undergoing laparoscopic cholecystectomy under general anesthesia (primary outcome). In addition, the changes in heart rate, mean arterial blood pressure, and systolic and diastolic blood pressure, at different time points of pneumoperitoneum, were evaluated. Adverse events, if any, were also observed.

MATERIALS AND METHODS

After obtaining approval from the institutional ethical committee, this prospective randomized controlled double-blind intervention study was conducted over a period of 1 year from January 2019 to December 2019 in elective general surgery operating room.

Inclusion criteria

Eighty patients of either sex, aged 20–50 years, American Society of Anesthesiologists (ASA) physical status classification I and II, scheduled for elective laparoscopic cholecystectomy under general anesthesia were included in this study.

Exclusion criteria

Unwilling patients, patients with uncontrolled blood pressure, severe renal, endocrine, cardiac dysfunction, heart block and on beta-blocker drugs, morbidly obese, pregnant, and lactating mothers were excluded from the study.

Sample size

From the literature Kholi et al.,[8] it is noted that MAP at 10 min after pneumoperitoneum was 96.43±9.08 and 100.47±10.96 in dexmedetomidine and clonidine groups, respectively. The pooled standard deviation was calculated to be 10. We assumed that detecting a minimum difference of 7 mmHg in MAP would be clinically relevant.

Setting the power of study at 80% and allowing α error of 5%, and replacing the values in the formula, the sample size was found to be 32 (approximated) in each group. Hence, 64 patients were needed assuming 1:1 group allocation. Considering a 20% dropout, the sample size was adjusted finally to 40 in each group.

Routine investigations were performed as per institutional protocol and as per patient's requirement. The study procedure was explained in details to all the participated

patients in their own vernacular language. Then written informed consent was obtained from each patient.

All patients were kept on fasting as per ASA guidelines and advised to take tab. alprazolam (0.5 mg) and tab. pantoprazole (40 mg) per orally in the previous night of surgery. Before taking patients inside the operating room, each patient was attended in the pre-operative room for repeat anesthetic checkup, pre-operative counseling, and obtaining written informed consent for the study.

The patients were randomly allocated into two groups to receive either inj. dexmedetomidine in saline (Group-D, n=40) or inj. clonidine in saline (Group-C, n=40) intravenous (i.v.) as pre-medication. "Sealed envelope" technique was used for randomization. This double-blind study was ensured by keeping the patients and the anesthesiology resident who was collecting data was kept unaware of the specific study drug that was administered to a specific group of patients (Figure 1).

On arrival in the operating room, monitors were attached. After noting baseline hemodynamic values and SpO_2, continuous monitoring of SpO_2, ECG, heart rate, systolic, diastolic, and mean arterial blood pressure was done. An i.v. line was secured with an 18G i.v. cannula and Ringer's lactate solution was started. Then, pre-medicated with inj. glycopyrrolate 4 mcg/kg; inj. midazolam 0.025 mg/kg. According to the code found in the envelope, the patients of two groups received study drugs as follows; Group-D received 1 mg/kg dexmedetomidine in normal saline and Group-C received 1 mg/kg clonidine in normal saline to make a total volume of 15 mL. The drugs were administered over a period of 10 min using a syringe pump and the infusion was completed 5 min before induction. The study drugs were prepared in identical syringes labeled with randomization numbers by an investigator who was neither involved in administration of the anesthesia nor in the follow-up of patients.

After pre-oxygenation with 100% oxygen for 3 min, anesthesia was induced with inj. propofol 2 mg/kg i.v. which was administered slowly till the loss of response to verbal commands. Inj. fentanyl 2 mcg/kg was used for analgesia. Inj. atracurium 0.5 mg/kg was administered i.v. to facilitate intubation at train of four (TOF) ratio of 0 and bispectral index (BIS) value of 40–60. Intubation was completed within 15 s and capnograph was attached. After confirming the position of the tube, maintenance of anesthesia was done with gas mixture of 33% oxygen in nitrous oxide. Volume-controlled ventilation with a tidal volume of 6–8 mL/kg and a ventilation rate of 12–16 breaths/min was used to maintain end-tidal CO_2 ($EtCO_2$) in the range of 35–40 mmHg. Maintenance of anesthesia was done using inj. atracurium (0.1 mg/kg) and inhalational agent isoflurane (0.5–1 volume%) to keep TOF ratio 0 and BIS value between 40 and 60.

CO_2 was insufflated into the peritoneal cavity at 2 l/min to create pneumoperitoneum. Intra-abdominal pressure was maintained at 12–14 mmHg throughout the laparoscopic procedure. After the pneumoperitoneum was established, ventilator settings were changed into pressure-controlled ventilation to maintain $EtCO_2$ in range of 35–40 mmHg, peak airway pressure below 40 cmH_2O, and mean airway pressure below 30 cmH_2O. Heart rate, systolic, diastolic, MAP, and SpO_2 were measured at different time points as follows: Before giving study drug (baseline), after giving study drug, before pneumoperitoneum, immediately after pneumoperitoneum, and thereafter, at 10, 20, 30, 40, and 50 min.

Throughout the procedure, fall in the MAP of ≥20% of the base value was countered by infusing 250 mL bolus Ringer's lactate solution and then, in addition, administering i.v. inj. mephentermine 3 mg, if required. Heart rate <50 beats per minute was treated with i.v. inj. atropine 0.6 mg. Any adverse events such as bradycardia, hypotension, and other complications were noted. Although the conducting anesthesiologist remained unaware of the exact study drug administered, no problem was faced in managing the adverse events. The reason is both the study drugs belongs to the same pharmacological class and similar type of adverse events.

Isoflurane was turned off when pneumoperitoneum was completely removed. At the end of operation, residual neuromuscular block was reversed by giving inj. neostigmine (0.05 mg/kg) and inj. glycopyrrolate (0.01 mg/kg). When patient's respiration became spontaneous and regular and they were able to obey simple commands and other recovery criteria were fulfilled, oropharyngeal suctioning and extubation (TOF 0.9) were done. Before discharging the patient from post-operative recovery room, achievement of modified Aldrete score of 9 was ensured for all patients.

Continuous data are expressed as mean±standard deviation (SD) and are analyzed using Student's *t*-test. Categorical data (Gender and ASA status) are expressed as number of patients and are analyzed using Chi-square test. The demographic parameters in both groups were not statistically significant. $P<0.05$ is statistically significant.

RESULTS

Demographic parameters and duration of surgery were comparable between the two groups (Table 1). Baseline

vital parameters before administering study drugs were also comparable (Tables 2-5).

Statistically significant difference was observed in heart rate among two groups (lower in dexmedetomidine group) constantly since giving study drug, immediately after creation of pneumoperitoneum, and then, at 10, 20, 30, 40, and 50 min after pneumoperitoneum.

Systolic, diastolic, and mean blood pressures were found to be significantly lowers in Group D (except after administering study drug) immediately after creating pneumoperitoneum, and 10, 20, 30, 40, and 50 min after pneumoperitoneum.

DISCUSSION

The present study finds that both the clonidine and dexmedetomidine when used before induction have yielded a good control of heart rate, systolic, diastolic, and MAP at different time points of intraoperative period. It was found that the use of dexmedetomidine has considerably lower heart rate responses immediately after the creation of pneumoperitoneum and then consistently at other time points such as 10, 20, 30, 40, and 50 min after pneumoperitoneum compared with those receiving clonidine. Similarly, better control was observed with the use of dexmedetomidine compared with clonidine regarding other parameters such as systolic, diastolic, and mean blood pressures.

Table 1: Demographic profile and duration of surgery

Profile	Group C (n=40)	Group D (n=38)	P-value
Male : Female	11:29	5:35	0.19
Age (Mean±SD)	32.7±8.43	31.4±6.88	0.452
ASA I : ASA II	28:12	31:9	0.157
Body weight (Mean±SD)	51.98±12.2	49.25±9.39	0.266
Duration of surgery (Mean±SD)	63±13.93	68±15.95	0.139

Data are presented here as Mean±Standard deviation (SD) and analyzed using t-test except gender distribution and ASA which are categorical data and presented as number of patients and analyzed using Chi-square test. Group D, patients receiving dexmedetomidine, Group C, patients receiving clonidine

Table 2: Heart rate changes

Timing	Group C (n=40) Mean±SD	Group D (n=40) Mean±SD	P-value
Before giving study drug	99.3±21.91	97.36±19.03	0.675
After giving study drug	75.83±13.29	67.53±9.39	0.002
Tx	95.4±17.4	74.7±11.69	<0.001
T-0	103.93±14.7	80.4±9.52	<0.001
T-10	92.37±10.9	79.4±7.58	<0.001
T-20	88.97±9.82	76.57±8.98	<0.001
T-30	87.86±6.88	74.41±10.07	<0.001
T-40	80.11±6.59	71.86±13.25	<0.001
T-50	79.48±5.87	69.34±12.31	<0.001

Tx: Before creating pneumoperitoneum, T-0: Immediately after pneumoperitoneum, T-10, T-20, T-30, T-40, T-50: 10, 20, 30, 40, 50 min after pneumoperitoneum, respectively. Data are presented in beats per minute. Analyzed using unpaired t-test

Table 3: Changes in systolic blood pressure

Timing	Group C (n=40) Mean±SD	Group D (n=40) Mean±SD	P-value
Before giving study drug	121.23±15.89	120±19.39	0.757
After giving study drug	116.17±18.09	110.23±10	0.074
Tx	112.63±9.18	108.33±7.32	0.02
T-0	136.27±14.84	126.93±14.35	0.005
T-10	132.8±16.52	122.9±14.29	0.005
T-20	130.33±14.99	120.4±15.16	0.004
T-30	129.07±18.34	118.15±17.84	0.009
T-40	127.17±21.5	116.64±20.03	0.026
T-50	124.54±19.17	113.04±18.62	0.008

Tx: Before creating pneumoperitoneum, T-0: Immediately after pneumoperitoneum, T-10, T-20, T-30, T-40, T-50: 10, 20, 30, 40, 50 min after pneumoperitoneum, respectively. Data are presented in mmHg. Analyzed using unpaired t-test

Table 4: Changes in diastolic blood pressure

Timing	Group C (n=40) Mean±SD	Group D (n=40) Mean±SD	P-value
Before giving study drug	76.33±8.48	76.37±9.85	0.985
After giving study drug	72.3±9.2	70.73±5.14	0.35
Tx	70.33±10.3	65.77±9.11	0.04
T-0	86.97±11.7	81.03±9.37	0.014
T-10	82.07±7.52	76.63±8.9	0.006
T-20	81.83±4.94	76.2±8.78	<0.001
T-30	80.96±6.2	73.11±9.42	<0.001
T-40	79.67±9.93	72.07±11.99	0.003
T-50	77.41±8.76	70.67±9.89	0.002

Tx: Before creating pneumoperitoneum, T-0: Immediately after pneumoperitoneum, T-10, T-20, T-30, T-40, T-50: 10, 20, 30, 40, 50 min after pneumoperitoneum, respectively. Data are presented in mmHg. Analyzed using unpaired t-test

Table 5: Changes in mean arterial blood pressure

Timing	Group C (n=40) Mean±SD	Group D (n=40) Mean±SD	P-value
Before giving study drug	91.47±8.19	90.63±8.59	0.656
After giving study drug	87.57±10.09	84.43±11.41	0.196
Tx	82.67±7.23	76.07±17.9	0.035
T-0	103.67±12.28	95.77±20.04	0.037
T-10	98.47±8.97	92.43±7.09	0.001
T-20	97.73±6.8	90.87±6.99	<0.001
T-30	94.06±7.5	88±7.21	<0.001
T-40	89.37±10.65	86.93±16.54	0.042
T-50	88.43±9.31	81.79±13.27	0.012

Tx: Before creating pneumoperitoneum, T-0: Immediately after pneumoperitoneum, T-10, T-20, T-30, T-40, T-50: 10, 20, 30, 40, 50 min after pneumoperitoneum, respectively. Data are presented in mmHg. Analyzed using unpaired t-test

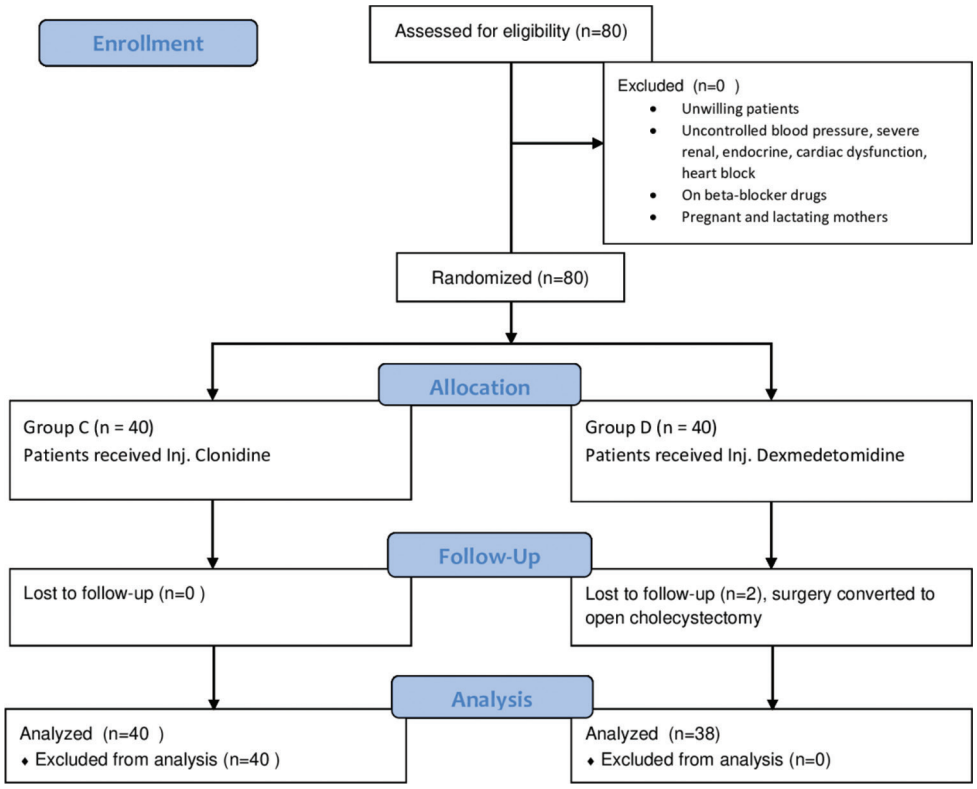

Figure 1: Consort flow diagram

Kumar et al.,[6] found that dexmedetomidine and clonidine are equally effective in attenuating the hemodynamic response to pneumoperitoneum without any significant adverse events. Bharti et al.,[2] evaluated clonidine infusion (3 μg/kg/h) and dexmedetomidine infusion (0.2 μg/kg/h) compared with control (normal saline). They observed that the use of clonidine has yielded considerable reduction of heart rate and comparable control of MAP in comparison with dexmedetomidine.[2] Overall, both drugs have shown favorable responses regarding intraoperative hemodynamics during laparoscopic cholecystectomy. Sharma et al.,[9] compared clonidine and dexmedetomidine both given at a dose of 1 μg/kg over 15 min, 30 min before the surgery. Patients receiving clonidine had better hemodynamic response compared with control (fentanyl) group. The hemodynamic stability was found to be better with dexmedetomidine compared with clonidine. Hatti et al.,[10] compared clonidine and dexmedetomidine at a dose of 1 μg/kg for 15 min along with pre-medication before induction. Both drugs were found to attenuate the hemodynamic responses at induction, during pneumoperitoneum, and at extubation in patients undergoing laparoscopic lower abdominal oncosurgeries effectively. The attenuation of hemodynamic responses was better controlled with dexmedetomidine than clonidine.[10] Other studies[11,12] also report about better control of heart rate in patients receiving dexmedetomidine compared with clonidine during intubation and pneumoperitoneum. Dexmedetomidine attenuates systolic blood pressure changes during pneumoperitoneum more effectively than clonidine when administered intravenously before induction.[12]

Basar et al.,[13] used 0.5 mcg/kg dexmedetomidine as a single pre-operative dose and found blunting of hemodynamic responses. Bhattacharjee et al.,[14] infused 0.2 mcg/kg/h dexmedetomidine and found significantly less MAP and heart rate throughout the period of pneumoperitoneum. Kalra et al.,[15] used clonidine 1 mcg/kg i.v over a period of 15 min before pneumoperitoneum and found significantly better hemodynamic response compared with the control group. Ghodki et al.,[16] used dexmedetomidine 1 mcg/kg i.v over 15 min before induction followed by maintenance infusion of 0.2 μg/kg/h and observed minimal change in BP with pneumoperitoneum.

In another study, dexmedetomidine (loading 1 μg/kg followed by infusion 0.6 μg/kg/h) was found to provide stable intraoperative hemodynamics during propofol-based anesthesia for laparoscopic cholecystectomy.[17] Dexmedetomidine was also found to reduce propofol requirement for induction as well as maintenance, without compromising recovery profile.[17]

In a dose-finding study, Ye et al.,[18] evaluated dexmedetomidine 0.4, 0.6, and 0.8 μg/kg. The heart rate,

systolic blood pressure, and diastolic blood pressure were found to be better controlled with the use of 0.6 and 0.8 μg/kg doses.[18] They also observed that intravenous infusion of 0.6 μg/kg dexmedetomidine before induction can maintain hemodynamic stability in patients undergoing laparoscopic cholecystectomy.[18] In the present study, comparatively a higher dose (1 μg/kg) was used without any serious adverse events.

Joris[3] reported that peritoneal insufflation (intra-abdominal pressure 14 mmHg) results in a significant increase (35%) of MAP, a significant reduction (20%) of cardiac index, and a significant increase of systemic (65%) and pulmonary (90%) vascular resistances. To determine the safe range of intra-abdominal pressure during laparoscopic surgery, Ishizaki et al.,[19] found that cardiac output was decreased significantly by 1 h after the start of insufflation and became progressively lower during the procedure. In the present study, intra-abdominal pressure was kept within the range of 12–14 mmHg during the course of pneumoperitoneum.

Limitations of the study

We have only checked the hemodynamic stress response during pneumoperitoneum. Hemodynamic surge during endotracheal intubation and extubation was not checked. Also the plasma cortisol level was not assessed as baseline and after pneumoperitoneum. It can be a future scope.

CONCLUSION

Intravenous dexmedetomidine is more efficacious than intravenous clonidine as pre-medication in attenuating hemodynamic stress responses in laparoscopic cholecystectomy surgeries.

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DM- Daily conduct, data collection, first draft; **SKH-** Daily conduct, data collection, first draft; **SD-** Assisting conduct of study, data analysis, first draft; **SN-** Assisting conduct of study, data analysis, first draft, revision of draft; **SC-** Concept, design, daily guidance, analysis, logical conclusion, revision of first draft; **SP-** Concept, design, daily guidance, analysis, logical conclusion.

Work attributed to:
Bankura Sammilani Medical College, Bankura, West Bengal, India.

Orcid ID:
Dr. Diptimay Majumder - https://orcid.org/0000-0001-9785-3533
Dr. Susanta Kumar Halder - https://orcid.org/0000-0003-2195-0390
Dr. Swarup Datta - https://orcid.org/0000-0002-1493-7270
Dr. Sruthi Naresh - https://orcid.org/0000-0002-7799-8687
Dr. Soma Chakraborty - https://orcid.org/0000-0003-0253-5183
Prof. Subrata Pahari - https://orcid.org/0009-0002-0931-2580

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