Bradycardia during laparoscopic surgeries: A cross-sectional study

Gautam B1, Maharjan A2, Ghimire S3
1Binod Gautam, Associate Professor; 2Ashmita Maharjan; 3Suson Ghimire, MD Resident, Department of Anaesthesiology and Intensive Care, Kathmandu Medical College Teaching Hospital, Kathmandu, Nepal.

Abstract

Background: Bradycardia occurring during laparoscopic surgery potentially leads to cardiac arrest and adverse outcomes. Apart from the vagal reflex for its genesis, the knowledge on frequency and risk factors is limited.

Objectives: To identify the bradycardia frequency and time points for its occurrence during laparoscopic surgeries.

Methodology: In this hospital-based cross-sectional study, anaesthesia-related incident reports on bradycardia were collected from January to December 2019. Bradycardias (heart rate less than 60/minute) that occurred during laparoscopic surgeries were analyzed to characterize patient factors, the time point for occurrence, circumstantial events, management strategies, and outcomes.

Results: Among 801 laparoscopic surgeries, 28 (3.4%) bradycardic incidents were identified, with one progressing to cardiac arrest. All bradycardias occurred in 26 patients undergoing laparoscopic cholecystectomy under general anaesthesia, with two patients each experiencing two bradycardic episodes. The mean patient age was 45 (±16.3) years and 17 (65.3%) were women. Fifteen (57.6%) patients had no co-morbidity. Controlled hypertension and hypothyroidism co-existed in seven (26.9%) and three (11.5%) cases respectively. Bradycardia occurred once each (3.5%) during laryngoscopy and endotracheal intubation. Six (21.4%) and twenty (71.4%) bradycardias respectively occurred before and during pneumoperitoneum. The mean of minimum heart rates was 43 (±8.8) per minute. Anticholinergics were administered in 25 (89.2%) incidents. Stopping surgery and pneumoperitoneum deflation included other major management strategies. The cardiac arrest case received chest compressions and adrenaline. Surgery resumed in all cases without adversity.

Conclusion: Bradycardia occurs during laparoscopic surgery, more frequently during pneumoperitoneum and in healthy and younger females. Immediate cessation of surgical stimuli and atropine administration possibly prevent bradycardia from progressing to cardiac arrest.

Key words: Bradycardia; Incident report; Laparoscopic surgery; Pneumoperitoneum; Vagal reflex.

INTRODUCTION

The laparoscopic approach being minimally invasive offers reduced pain, improved pulmonary function, and early recovery after surgery. It has become the standard of care for various procedures in gynaecological, urological, and general surgical specialties. However, serious intraoperative complications inherent to laparoscopic surgery including vascular injury, gas embolism, arrhythmias and cardiac arrest have been reported1–3.

Reflex bradycardia, owing to vagal response during abdominal surgeries is a well-known entity4. The incidence of laparoscopy-induced bradycardias has been reported to range widely between 3.4 and 28% of cases5–7. A recent study has analyzed bradycardia occurring during pneumoperitoneum created for laparoscopic surgeries, as an early warning sign of cardiac...
Cases of intra-operative cardiac arrests have been reported to instantaneously follow the bradycardias appearing during various phases of laparoscopic surgeries\(^2\)\(^3\). The challenges of preventing and managing bradycardia during laparoscopic surgeries and avoiding its adverse consequences while the patients are under the influence of anaesthesia remain. However, there is no clear estimate of the incidence of bradycardia during laparoscopic surgery in our population.

This study primarily aimed to identify the bradycardia frequency and the time point for its occurrence during laparoscopic surgeries, by analyzing the anaesthesia-related incident reports on bradycardia collected over the calendar year 2019.

**METHODOLOGY**

This was a cross-sectional study conducted from January to December 2019 in the setting of operating rooms of Kathmandu Medical College Teaching Hospital, with the introduction of reporting on anaesthesia-related incidents at our department. Incident reports that comprised bradycardia as the event, which occurred during laparoscopic surgeries were included. The study was designed to identify the clinical patterns of bradycardia occurrence during the laparoscopic surgeries. An approval from the Institutional Review Committee of Kathmandu Medical College (Ref: 231120187) and informed written consent from the patients were obtained.

The study tool comprised of a paper form, which contained fields to record the characteristics of the patient, anaesthesia, and surgery, and patient outcomes including cardiac arrest, Intensive Care Unit admission, and/or mortality. Blank space was made available for illustrating a narrative of each incident. The forms were filled and reported voluntarily by the MD Anaesthesiology residents, who witnessed the incident.

The identified reports were scrutinized to confirm bradycardia (heart rate less than 60/minute) for inclusion in the analysis. The time point of bradycardia occurrence concerning anaesthetic and/or surgical phase was recorded and presented as a number (percentage). Patients’ age was stratified on an interval of 10 years and presented as a mean (standard deviation) and range.

From the written narratives, key events surrounding each bradycardic incident were identified and recorded. The lowest heart rate (HR) witnessed during the incident was stratified on an interval of five and presented as a mean (standard deviation) and range. Management strategies undertaken were examined and ordered in a temporal sequence. Medications administered and patient responses were also recorded. All the incidents were analyzed for any underlying common denominators and were studied for the presence of possible patterns.

**RESULTS**

Among 801 laparoscopic surgeries, 647 (80.77%) comprised of laparoscopic cholecystectomies, 40 (4.99%) gynecologic surgeries, 15 (1.87%) urologic surgeries, and 99 (12.35%) other gastrointestinal procedures. Twenty-six patients were identified, in whom 28 (3.4%) bradycardic incidents were confirmed and analyzed. Out of 26 patients, two patients each had two episodes of bradycardia. All bradycardias occurred during elective laparoscopic cholecystectomy performed under general anaesthesia. One case progressed to cardiac arrest and received Intensive Care monitoring postoperatively, but there were no reported deaths.

Mean (standard deviation) patient age was 45 (16.3), which ranged between 15 and 72 years. Twenty (76.9%) patients aged 60 years or less (Table 1).

The most common co-morbidities comprised of hypertension and hypothyroidism. One patient had pre-existing sinus bradycardia with HR of 44/minute, but none had known cardiac disease or symptoms. This particular patient, although did have a normal HR with the start of anaesthesia, suffered bradycardia later during surgery. All patients had continued their regular medications till before appearing for surgery and none of them received prophylactic anticholinergics.

Agents used for anaesthesia induction were reported in 14 patients, all of whom received a combination of propofol and vecuronium. Fentanyl was used in all except for one, who received pethidine. Low dose ketamine and lignocaine were administered intravenously in three and one cases respectively. The carbon dioxide flow rate was reported in six cases as 1.5, 2, 2, 2.8, 3, and 6 liters per minute. Intra-abdominal pressure at the moment of bradycardia occurrence was reported in three cases as 10, 12, and 14 mmHg.

The majority of bradycardias, 20 (71.4%) occurred during pneumoperitoneum (Table 2).

Laryngoscopy-induced bradycardia occurred in one case that reverted on its own with laryngoscope removal. Another case occurred immediately after endotracheal intubation. In these two cases, bradycardia occurred during pneumoperitoneum. Other preceding
events included un-anticipated difficult endotracheal intubation (more than three attempts for a success) along with esophageal intubation in two cases, in whom bougie-guidance was ultimately successful. Un-intended esophageal intubation was witnessed in further two cases that required bougie-guidance and stylet-use in one each. Cardiac arrest, second-degree heart block, hypotension, and hypertension comprised the succeeding events reported for one (3.5%) case each.

Minimum witnessed HR ranged between 23 and 57, with a mean (standard deviation) of 43.1 (8.87) per minute. It was 45/minute or less during 17 (60.7%) of the incidents (Table 3).

Corrective medications were used for all bradycardias, except for the two that occurred during laryngoscopy and intubation. The temporal sequence of management strategies showed that anticholinergic (atropine or glycopyrrolate) administration was the most frequent primary response in 15 (57.6%) of the incidents (Table 4). Anticholinergics were administered during 25 (89.2%) of the bradycardic incidents but one was dealt with mephenteramine 15 milligrams (mg) for the concurrent hypotension (Figure 1).

Atropine was administered as the first-choice anticholinergic in 19 (76%) incidents, out of which 15 (78.9%) got corrected with a single-dose. Among six (24%) cases receiving glycopyrrolate, four (66.6%) recovered with the single-dose.

Bradycardia with HR of 30/minute and the inability to palpate peripheral pulses immediately on trochar insertion were reported in the cardiac arrest case. In this case, removal of the trochar, atropine administration, chest compressions (20 seconds), and adrenaline (40 micrograms) proved to be effective. All patients recovered from bradycardia and succeeding events. Intended surgery was accomplished and the course thereafter was uneventful in all of them.

Table 1: Patient characteristics (n=26).

| Variable          | Stratum          | Number |
|-------------------|------------------|--------|
| Age (years)       | 11 to 20         | 2      |
|                   | 21 to 30         | 2      |
|                   | 31 to 40         | 9      |
|                   | 41 to 50         | 2      |
|                   | 51 to 60         | 5      |
|                   | 61 to 70         | 5      |
|                   | 71 to 80         | 1      |
| Gender            | Female           | 17     |
|                   | Male             | 9      |
| ASA physical status class | I          | 15     |
|                   | II               | 11     |
| Co-morbidities*   | None             | 15     |
|                   | Hypertension     | 7      |
|                   | Hypothyroidism   | 3      |
|                   | Diabetes mellitus| 1      |
|                   | Bronchial asthma | 1      |
|                   | Sinus bradycardia| 1      |
|                   | HBsAg positive status | 1 |
| Pre-operative medications* | None | 15 |
|                   | Atenolol         | 3      |
|                   | Amlodipine       | 3      |
|                   | Losartan         | 2      |
|                   | Thyroid hormone  | 3      |
|                   | Hydrochlorothiazide | 1    |
|                   | Pregabalin       | 1      |

ASA: American Society of Anesthesiologists; HBsAg: Hepatitis B surface antigen; *single case may have more than one attribute
Table 2: Timepoint for bradycardia occurrence (n=28).

| Timepoint                                                | Frequency (%) |
|----------------------------------------------------------|---------------|
| Laryngoscopy                                             | 1 (3.5)       |
| Endotracheal intubation                                  | 1 (3.5)       |
| Before abdominal insufflation                            |               |
| • Primary port creation                                  | 2 (7.1)       |
| • Trochar placement                                      | 4 (14.2)      |
| During abdominal insufflation (pneumoperitoneum)         |               |
| • Initiation of carbon dioxide insufflation              | 5 (17.8)      |
| • Before surgical manipulation of the gall bladder       | 12 (42.8)     |
| • Surgical dissection around the gall bladder            | 3 (10.7)      |

Table 3: Minimum witnessed heart rate (n=28).

| Heart rate (per minute) | Count (n) |
|-------------------------|-----------|
| 21 to 25                | 2         |
| 26 to 30                | 2         |
| 31 to 35                | 2         |
| 36 to 40                | 3         |
| 41 to 45                | 8         |
| 46 to 50                | 5         |
| 51 to 55                | 5         |
| 56 to 60                | 1         |

Table 4: Temporal sequence of management strategies (n=26).

| Order | Management strategies          | Count (n) |
|-------|--------------------------------|-----------|
| First | Atropine administration        | 9         |
|       | Glycopyrrolate administration  | 6         |
|       | Stop carbon dioxide flow       | 6         |
|       | Stop surgery                   | 3         |
|       | Pneumoperitoneum deflation     | 2         |
| Second| Atropine administration        | 5         |
|       | Pneumoperitoneum deflation     | 4         |
|       | Stop surgery                   | 3         |
|       | Chest compression              | 1         |
|       | Mephenteramine administration  | 1         |
| Third | Atropine administration        | 8         |
|       | Glycopyrrolate administration  | 1         |
|       | Adrenaline administration      | 1         |
|       | Stop carbon dioxide flow       | 1         |
| Fourth| Adrenaline administration      | 1         |

DISCUSSION

The study highlights the importance of bradycardia during laparoscopic surgeries, in terms of its frequent occurrence in younger, and otherwise fit and healthy females. One of the most commonly associated findings comprised peritoneal stretching related to the port creation, trochar insertion or pneumoperitoneum. Besides, majority bradycardias responded well to the anticholinergics and withdrawal of surgical stimuli, implying vagal reflex for the underlying mechanism.

Bradycardia originates mostly from sinoatrial nodal dysfunction or atrioventricular block. Possible extrinsic causes are often reversible and are related to drugs or autonomic nervous system influences. Vagal stimulation, sympatholytics, beta-blockers, calcium channel blockers, opioids, hypothyroidism, hypothermia, increased intracranial pressure and endotracheal suctioning have all been depicted for bradyarrhythmias. One or more of these factors might be implicated during laparoscopic surgeries. The co-morbidities reported in our patients including hypertension and diabetes mellitus may also have a role to play, specifically the use of beta-blockers in the former condition and possibility of autonomic dysfunction in the latter condition.

Laparoscopic cholecystectomy comprising 81% of laparoscopic surgeries in our set up was the probable reason for bradycardias being exclusively associated with it. No bradycardia occurred during urologic surgeries, which might imply that extraperitoneal laparoscopic surgeries are less likely to predispose bradycardia, in addition to a very small cohort of urologic surgeries in the study. Less intense peritoneal stretching in these surgeries might be accountable, even if they are comparatively time-consuming procedures.

Laparoscopic cholecystectomy comprising 81% of laparoscopic surgeries in our set up was the probable reason for bradycardias being exclusively associated with it. No bradycardia occurred during urologic surgeries, which might imply that extraperitoneal laparoscopic surgeries are less likely to predispose bradycardia, in addition to a very small cohort of urologic surgeries in the study. Less intense peritoneal stretching in these surgeries might be accountable, even if they are comparatively time-consuming procedures.

The bradycardias were mostly related to but not limited to pneumoperitoneum. These findings are similar to previous studies. Peritoneal stretching and stimulation are unavoidable while creating an entry during intraperitoneal laparoscopic surgeries; and, with pneumoperitoneum, the most intense cardiac impacts are shown to occur during the initial three minutes of carbon dioxide insufflation. This underscores the carefulness required during the early surgical phases notably port creation, trochar insertion, and abdominal...
insufflation, and preparedness to withdraw any of the stimuli whenever necessary. Also, the high carbon dioxide flow rate may be an important culprit. Although no reports in our study mentioned technical difficulties relating to insufflation, it is also crucial that insufflating machines are regularly tested and maintained. A slower initial insufflation and maintenance of lowest acceptable intra-abdominal pressure are ever preferable, even if achieving a flow rate of 4-6 liters per minute with a pressure up to 10-15 mmHg is the usual practice.

The commonest association was general anaesthesia, which is considered the current standard for laparoscopic surgeries, even though regional techniques have been utilized for selected patients. However, GA increases the vagal tone, especially the combination of propofol, vecuronium, and fentanyl that constituted the mainstay of induction agents in our patients. Fentanyl reduces sympathetic tone and enhances vagal tone, more so with the concurrent use of vecuronium, potentially leading to bradycardia and cardiac arrest. As there is a lack of controlled trials comparing different induction agents for bradycardia predisposition, we may not recommend any specific choice of agents for patients undergoing laparoscopic surgeries. Activation of vagal reflex with the airway manipulation and vagotonic drugs were the most likely contributors to bradycardias, which occurred during laryngoscopy and intubation in the study.

When endotracheal intubation proves difficult, the circumstantial events including repeated airway manipulations, esophageal intubation, additional induction agents, and tracheal irritation potentially exist. Importantly, the un-intended esophageal intubation seemed to be associated with bradycardia in four of our cases, even though capnography was used in all cases and esophageal intubations were detected immediately with a consequent minimum distension of stomach. The physical presence of air distending the stomach and activating the stretch receptors to provoke vagal reflex is a possibility.

---

**Figure 1:** Medication use and outcome (values are number of incidents).

- All bradycardias (28)
- No Medication administered (2)
- Recurrence (2)
- Medication administered (26)
- No anticholinergic (25)
- Resumed surgery (2)
- Glycopyrrolate 0.2 mg (6)
- Ineffective response (2)
- Atropine 0.6 mg (1)
- Second-dose Atropine (2)
- Adrenaline 10 mcg (1)
- Chest compressions+Adrenaline (1)
- Effective first-dose Atropine (15)
- Effective first-dose Glycopyrrolate (4)
- Effective response (2)
- Resumed surgery (1)
- No recurrence (1)
- No cardiac aftermath (1)
The minimum reported HR was 45/minute or less among 60% of the incidents, which corresponds with a previous study\(^5\). Its wide range between 23 and 57/minute might reflect varying treatment thresholds or time-lag for the effects of treatment. However, the rate of our pharmacological intervention was much higher compared to a previous study, in which only 23% of such incidents were medicated\(^5\). Anticholinergic administration was the first measure taken in the majority (57%) of incidents and it was performed during 89% of the incidents in the end. Seemingly, this might imply that non-pharmacologic intervention which were mentioned as the first measure in 43% of incidents were not effective. However, in such crisis scenarios, interventions taken are usually simultaneous and non-exclusive, leading to possible combined effects; and, as our objective did not include to compare the effectiveness among the interventions, we are not in position to infer definitely that non-pharmacologic measures do not have any role in reverting bradycardias. Understandably, anaesthesiologists seem to get a sense of control over the situation in administering corrective medications. The timing and selection of agents, however, primarily depends on the ongoing events, together with the care provider’s experience and preferences. Furthermore, the lack of local protocols might account for the non-uniformity in management options, including the selection among anticholinergics. Efficacy and rapidity of action might point towards preferring atropine over glycopyrrolate for correcting intraoperative bradycardias\(^2,14\). Relatively more frequent requirements for the second-dose in patients who received glycopyrrolate as the first-choice anticholinergic possibly supports the atropine use, which was the most frequent pattern in our patients.

Progression to cardiac arrest in our single case might imply the appropriate response in administering anticholinergics and in communicating with the surgeon to immediately cease surgical stimuli and carbon dioxide flow, and to deflate the pneumoperitoneum. The interventions used and the manner they were implemented probably attributed to minimizing the cardiac arrest frequency. Multiple and simultaneous tasks are usual during anaesthetic crises, which might account for variations while reporting the sequence of management options. Also, the temporality of intervention is mostly determined by the time point for the incident occurrence. For instance, the first appropriate response to bradycardias during the port creation and trochar insertion would be removing the same stimulus, rather than deflating the pneumoperitoneum, which has not already been created.

More than one-third of the cases belonged to the age group of 31 to 40, and only six (23%) aged over 60 years. The females comprised 65% of the cases. An inherent high vagal tone described for younger individuals and females might be responsible\(^17,18\). Besides, undiagnosed pre-existing autonomic dysfunction might determine the HR responses during anaesthesia. All in all, some individuals might be quite special, in that their vagal responses are easily and/or excessively provoked. But, the unpredictability arises from the fact that the exact cause is often unknown. Pre-operative analysis of HR variability may be useful in identifying some of the at-risk individuals. Keen observation on the surgical steps and warning signs thus remains fundamental, as intra-operative bradycardia is not always an unpredictable occurrence. This is emphasized by three of our patients, in whom recurrence was observed after their bradycardias during the respective phases of pre-induction, laryngoscopy, and endotracheal intubation remained unmedicated.

The frequency of bradycardia (3.4%) during laparoscopic surgeries in our study resembles a previous retrospective study\(^5\). The calculated frequency of 4.3% bradycardia during our laparoscopic cholecystectomies approximates to a previous study\(^6\). Despite the improvements in patient preparation, surgical techniques and anaesthetic management, bradycardias are still encountered during laparoscopic surgeries. To avoid the possible disappointments that it brings, even in seemingly healthy individuals, bradycardia should be taken seriously. Knowing the procedure and a preparedness to act promptly is key, but not always enough. Non-technical skills including team working, situation awareness, and decision making at the individual level are crucial. And, if any risk factor is evident, it is prudent to administer an anticholinergic prophylactically. Some authors even recommend prophylactic anticholinergic for all laparoscopic patients\(^7\). But, the paucity of evidence for benefits in terms of numbers needed to prevent bradycardia along with the potential complications, do not suggest routine prophylaxis\(^19\).

Clinician-initiated self-reporting systems are considered transparent, reliable, and faithful for studying adverse events\(^10\). Even though causal relationship cannot be established with the study’s design, it has provided us with the opportunity to review possible preventive and corrective strategies. However, voluntary reporting and the absence of electronic record-keeping inevitably lead to an underestimation of the bradycardia frequency, which constituted the major limitation of the study. Minimum reportings on carbon dioxide insufflation rate
and intra-abdominal pressure during the procedure are accepted as further limitations to our study.

CONCLUSION

Bradycardia occurs during laparoscopic surgery, and mostly during peritoneal stretching, with the contribution from vagotonic drugs used for general anaesthesia. Anticipation and prophylactic anticholinergic use in selected cases, seriousness regarding the procedure, vigilant monitoring, and prompt action are emphasized.

Communicating with the surgeon to immediately cease the surgical stimulus, interrupt the carbon dioxide insufflation and deflate the pneumoperitoneum, concurrently with atropine administration relieves bradycardia and possibly prevent its progression to cardiac arrest.

Conflict of interest: None
Source(s) of support: None

REFERENCES

1. Krishnakumar S, Tambe P. Entry complications in laparoscopic surgery. J Gynecol Endosc Surg. 2009 Jan;1(1):4-11. [PubMed | DOI]
2. Biswas TK, Pembroke A. Asystolic cardiac arrest during laparoscopic cholecystectomy. Anaesth Intensive Care. 1994 Jun;22(3):289-91. [PubMed | Full Text | DOI]
3. Gautam B, Shrestha BR. Cardiac arrest during laparoscopic cholecystectomy under general anaesthesia: a study into four cases. Kathmandu Univ Med J. 2009 Jul-Sep;7(27):280-8. [PubMed | Full Text | DOI]
4. Doyle DJ, Mark PW. Reflex bradycardia during surgery. Can J Anaesth. 1990 Mar;37(2):219-22. [PubMed | Full Text | DOI]
5. Dabush-Elisha I, Goren O, Herscovici A, Matot I. Bradycardia during laparoscopic surgeries: a retrospective cohort study. World J Surg. 2019 Jun;43(6):1489-96. [PubMed | Full Text | DOI]
6. Reed DN Jr, Duff JL. Persistent occurrence of bradycardia during laparoscopic cholecystectomies in low-risk patients. Dig Surg. 2000;17(5):513-7. [PubMed | DOI]
7. Aghamohammadi H, Mehrabi S, Mohammad Ali Beigi F. Prevention of bradycardia by atropine sulfate during urologic laparoscopic surgery under general anesthesia: a randomized controlled trial. Urol J. 2009;6(2):92-5. [PubMed | Full Text]
8. Yong J, Hibbert P, Runciman WB, Coventry BJ. Bradycardia as an early warning sign for cardiac arrest during routine laparoscopic surgery. Int J Qual Health Care. 2015 Dec;27(6):473-8. [PubMed | Full Text | DOI]
9. Tomaselli GF. The bradyarrhythmias. In: Fauci AS, Braunwald E, Kasper DL, et al., editors. Harrison’s principles of internal medicine. 17th ed. Vol. 2. New York: McGraw Hill; c2008. p. 1416-24. [ISBN: 9780071544863]
10. Branche PE, Duperrut SL, Sagnard PE, Boulez JL, Petit PL, Viale JP. Left ventricular loading modifications induced by pneumoperitoneum: a time course echocardiographic study. Anesth Analg. 1998 Mar;86(3):482-7. [PubMed | Full Text | DOI]
11. Larsen JF, Svendsen FM, Pedersen V. Randomized clinical trial of the effect of pneumoperitoneum on cardiac function and haemodynamics during laparoscopic cholecystectomy. Br J Surg. 2004 Oct;91:848-54. [PubMed | DOI]
12. Jung KT, Kim SH, Kim JW, So KY. Bradycardia during laparoscopic surgery due to high flow rate of CO2 insufflation. Korean J Anesthesiol. 2013 Sep;65(3):276-7. [PubMed | Full Text | DOI]
13. Rucklidge M. General surgery. In: Allman KG, Wilson IH, editors; O'Donnell A, assistant editor. Oxford handbook of anaesthesia. 3rd ed. Oxford: Oxford University Press; c2011. p. 535-67. [ISBN: 9780199654468]
14. Joris JL. Anesthesia for laparoscopic surgery. In: Miller RD, editor; Fleisher LA, Johns RA, Savarese JJ, Wiener-Kronish JP, Young WL, consulting editors. Miller’s anesthesia. 6th ed. Vol. 2. Philadelphia: Elsevier; c2005. p. 2285-2306. [ISBN: 9780443066184]
15. Cozanitis DA, Erkola O. A clinical study into the possible intrinsic bradycardic activity of vecuronium. Anaesthesia. 1989 Aug;44(8):648-50. [PubMed | Full Text | DOI]
16. Barret KE, Barman SM, Boitano S, Brooks HL. Ganong’s review of medical physiology. 24th ed. New York: McGraw Hill; c2012. Chapter 25, Overview of gastrointestinal function & regulation; p. 455-75. [ISBN: 9781259027536]
17. Abhishek HA, Nisarga P, Kisan R, Mehganha A, Chandran S, Trichur R, et al. Influence of age and gender on autonomic regulation of heart. J Clin Monit Comput. 2013 Jun;27(3):259-64. [PubMed | DOI]
18. Huikuri HV, Pikkujamsa SM, Airaksinen KE, Ikahelmio MJ, Rantala AO, Kauma H, et al. Sex-related differences in autonomic modulation of heart rate in middle-aged subjects. Circulation. 1996 Jul;94(2):122-5. [Full Text | DOI]
19. Steer AE, Ozcan J, Emeto TI. The role of anticholinergic medication in the prevention of bradycardia during laparoscopic gynaecological surgery. Aust N Z J Obstet Gynaecol. 2019 Dec;59(6):777-80. [PubMed | DOI]

20. Katz RI, Lagasse RS. Factors influencing the reporting of adverse perioperative outcomes to a quality management program. Anesth Analg. 2000 Feb;90(2):344-50. [PubMed | Full Text | DOI]