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ORIGINAL ARTICLE**Clinical Trials Study**

- 1** Freehand-robot-assisted laparoscopic colorectal surgery: Initial experience in the Trinidad and Tobago
Cawich SO, Singh Y, Naraynsingh V, Senasi R, Arulampalam T

CASE REPORT

- 8** Rare case of perforated giant gastric ulcer with concurrent thyroid storm: A case report
Wang JX, Soh LS, Mahendran DCJ, Woon CY, Chia CLK

ABOUT COVER

Editorial Board Member of *World Journal of Surgical Procedures*, Meer M Chisthi, MS, PhD, Professor, Department of General Surgery, Government Medical College, Trivandrum, Kerala 695011, India.
meerchisthi.m@tmc.kerala.gov.in

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Clinical Trials Study

Freehand-robot-assisted laparoscopic colorectal surgery: Initial experience in the Trinidad and Tobago

Shamir O Cawich, Yardesh Singh, Vijay Naraynsingh, Ramdas Senasi, Tan Arulampalam

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Abstract

BACKGROUND

Laparoscopic colorectal surgery is still developing in the Anglophone Caribbean, having been first performed in the region in the year 2011. We report the initial outcomes using a robot camera holder to assist in laparoscopic colorectal operations.

AIM

To report our initial experience using the FreeHand® robotic camera holder (Freehand 2010 Ltd., Guildford, Surrey, United Kingdom) for laparoscopic colorectal surgery in Trinidad & Tobago.

METHODS

We retrospectively collected data from all patients who underwent laparoscopic colorectal resections using the Freehand® (Freehand 2010 Ltd., Guildford, Surrey, United Kingdom) robotic camera holder between September 30, 2021 and April 30, 2022. The following data were recorded: patient demographics, robotic arm setup time, operating time, conversions to open surgery, conversions to a human camera operator, number and duration of intra-operative lens cleaning. At the termination of the operation, before operating notes were completed, the surgeons were administered a questionnaire recording information on ergonomics, user-

difficulty, requirement to convert to a human camera operator and their ability to carry out effective movements to control the robot while operating.

RESULTS

Nine patients at a mean age of 58.9 ± 7.1 years underwent colorectal operations using the FreeHand robot: Right hemicolectomies (5), left hemicolectomy (1), sigmoid colectomies (2) and anterior resection (1). The mean robot docking time was 6.33 minutes (Median 6; Range 4-10; SD ± 1.8). The mean duration of operation was 122.33 ± 78.5 min and estimated blood loss was 113.33 ± 151.08 mL. There were no conversions to a human camera holder. The laparoscope was detached from the robot for lens cleaning/defogging an average of 2.6 ± 0.88 times per case, with cumulative mean interruption time of 4.2 ± 2.15 minutes per case. The mean duration of hospitalization was 3.2 ± 1.30 days and there were no complications recorded. When the surgeons were interviewed after operation, the surgeons reported that there were good ergonomics (100%), with no limitation on instrument movement (100%), stable image (100%) and better control of surgical field (100%).

CONCLUSION

Robot-assisted laparoscopic colorectal surgery is feasible and safe in the resource-poor Caribbean setting, once there is appropriate training.

Key Words: Laparoscopic; Robotic; Minimally invasive; Colorectal

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Core Tip: This study demonstrates that robot-assisted laparoscopic colorectal surgery is feasible in the resource poor Caribbean setting, but requires appropriate user training to ensure safe introduction of the technology.

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INTRODUCTION

Cooperman *et al*[1] were first to report laparoscopic colectomy for neoplastic disease in 1991. After this success, multiple reports of laparoscopic colectomies appeared in the surgical literature and the technique became widely accepted as the preferred approach for colorectal resections[2-9]. The benefits of laparoscopic colectomy are supported by level I data from the Barcelona trial[2], Clinical Outcomes of Surgical Therapy trial[3], Colon Cancer Laparoscopic or Open Resection trial[4] and the Conventional *vs* Laparoscopic assisted Surgery in Patients with Colorectal Cancer (MRC CLASICC) trial[5]. These trials and subsequent meta-analyses demonstrated laparoscopic colectomy's superiority over open colectomy in post-operative pain, return of bowel function and hospitalization[2-9].

In the Anglophone Caribbean, Plummer *et al*[10] first reported a series of laparoscopic colectomies in the year 2011, approximately 20 years after the first report by Cooperman *et al*[1]. We report our initial experience using the FreeHand® robotic camera holder (Freehand 2010 Ltd., Guildford, Surrey, United Kingdom) for laparoscopic colorectal surgery in Trinidad & Tobago.

MATERIALS AND METHODS

In this study we retrospectively collected data from hospital records of all patients who underwent laparoscopic colorectal resections using the Freehand® (Freehand 2010 Ltd., Guildford, Surrey, United Kingdom) robotic camera holder over a four-month period from September 30, 2021 to April 30, 2022. We excluded patients who were below 18 years of age, who underwent emergency operations, who had colectomies associated with other major procedures performed at the same sitting and those who did not consent to data collection.

For all patients who underwent colectomies, we recorded the following data: patient demographics, robotic arm setup time (time for draping, lens fixation and positioning), operating time, conversions to

open surgery, conversions to a human camera operator, number and duration of intra-operative lens cleaning. All data were entered into an excel database and the data were analyzed using Statistical Product and Service Solutions version 20.0.

In this series, the decision on operating room setup was taken at the pre-operative time out. In all cases, a 12 mmHg pneumoperitoneum was created using Hasson's technique *via* a port placed at the umbilicus. For a right hemicolectomy, the patient was placed supine and the left hand was tucked in. The laparoscopic monitors were placed on the right side of the patient and the Freehand robot was fixated to the right-side bed rail (Figure 1A). For a left hemicolectomy, the patient was placed supine and the right hand was tucked in. The laparoscopic monitors were placed on the left side of the patient and the robot was fixated to the left-side bed rail (Figure 1B). For an anterior resection, the patient was placed in reversed trendelenburg position and the both hands were tucked in. The laparoscopic monitors were placed at the patient's feet and the Freehand robot was fixated to the left-side bed rail (Figure 1C). A three-port technique was used in these cases and the 5 mm port sites were chosen by the operating surgeon based on his ergonomics. Once ports were placed, the robot was positioned and the operation commenced.

The operations were performed using the medial-to-lateral approach. The ureters were identified and preserved prior to mesenteric vascular control. Once sufficiently mobilized the colon was transected and an anastomosis completed. The specimen was exteriorized through a site chosen by the surgeon using a wound protector. Following local fast-track protocols, all patients were offered normal diet once awake. Urethral catheters were removed and the patients mobilized on post-operative day 1. The patients were discharged once they remained well and tolerated diet.

At the termination of the operation, before operating notes were completed, the surgeons were administered a questionnaire to solicit their subjective impression of the Freehand system. The questionnaire sought information on ergonomics, user-difficulty, requirement to convert to a human camera operator and their ability to carry out effective movements to control the robot while operating.

RESULTS

Over the study period, nine patients underwent colorectal operations using the FreeHand robot (Freehand 2010 Ltd., Guildford, Surrey, United Kingdom). There were three females and six males at an average age of 58.9 years (Median 60; Range 49-70; SD \pm 7.1). These patients underwent right hemicolectomies (3), extended right colectomies (2), left hemicolectomy (1), sigmoid colectomies (2) and anterior resection (1). The mean robot docking time was 6.33 min (Median 6; Range 4-10; SD \pm 1.8).

Intra-operatively, there were no conversions recorded and no adverse events encountered. The mean duration of operation was 122.33 min (Median 100; Range 84-330; SD \pm 78.5) and mean estimated blood loss was 113.33 mL (Median 50; Range 10-500; SD \pm 151.08). Specifically related to the intra-operative handling of the robot, there were no instances of conversion to a human camera holder. The laparoscope was detached from the robot for lens cleaning/defogging an average of 2.6 times per case (Median 3; Range 1-4; SD \pm 0.88), with cumulative mean interruption time of 4.2 min per case (Median 4; Range 1-8; SD \pm 2.15).

Post-operation, there were no complications or deaths. The mean duration of hospitalization was 3.2 d (Median 3; Range 2-6; SD \pm 1.30). Histologic assessment revealed adequate oncologic targets: 19.8 cm mean proximal margin distance (median 20, range 12-35, SD \pm 7.19), 17.22 cm mean distal margin distance (median 18, range 10-20, SD \pm 3.42), and 13 mean node harvest (median 12, range 10-18, SD \pm 2.55). All patients were alive and disease free after a mean follow-up of 5.1 mo. However, this duration of follow-up was not sufficient to meaningfully assess overall survival or disease-free survival. Three advanced laparoscopic surgeons performed these operations. When the surgeons were interviewed after operation, the surgeons reported that there were good ergonomics (100%), with no limitation on instrument movement (100%), stable image (100%) and better control of surgical field (100%).

DISCUSSION

Generally, the Anglophone Caribbean lagged behind the developed world in terms of adopting advanced operative techniques due to a combination of resource unavailability, financial limitations and leadership deficiencies[11]. To illustrate this, consider the fact that the initial report on laparoscopic colectomies from the Caribbean[10] came 20 years after it was first reported by Cooperman *et al*[1].

Similarly, the first report of robotic colectomy was published by Weber *et al*[12] in March, 2001. They reported two cases in which they used the DaVinci robotic platform (Intuitive Surgical Inc, Sunnyvale, California, United States) to perform a sigmoid colectomy for diverticulitis and a right hemicolectomy for diverticulitis. In the next few years, several reports of robotic colectomies began to appear in the surgical literature for benign and malignant disease[13,14]. However, robotic surgery remained dormant in the Anglophone Caribbean[15]. To the best of our knowledge, there has been no report of colorectal resections using the DaVinci or any other full robotic platform from the Caribbean. The first step toward

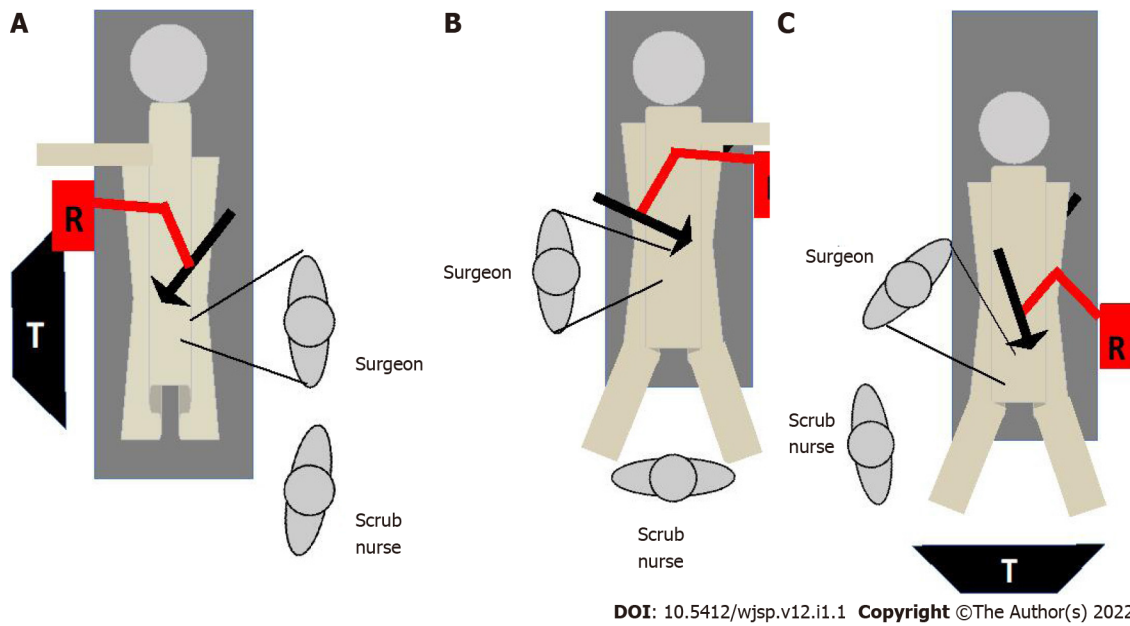


Figure 1 Operating room setup using the FreeHand (R) surgical robot. A: The operating room is setup for a right hemicolectomy, with the patient supine and the left hand tucked in. The laparoscopic stack (T) and the robot (R) are placed at the right side of the bed, while the surgeon and scrub nurse stand at the patient's left side; B: The operating room is setup for a left hemicolectomy, with the right hand tucked in and the robot (R) and laparoscopic stack (T) at the patient's left; C: For an anterior resection, the patient is in a reversed trendelenburg position with both hands tucked in. The robot (R) is fixated to the left bed rail and the stack at the patient's feet.

robotics in the Caribbean was a FreeHand robot-assisted laparoscopic right hemicolectomy performed on November 29, 2021. To illustrate our point once more, this was two decades after robotic hemicolectomy was first described by Weber *et al*[12].

In the report by Weber *et al*[12] the DaVinci robot (Intuitive Surgical Inc, Sunnyvale, California, United States) was utilized. However, there are no da Vinci platforms in any nation in the Anglophone Caribbean. It is a resource-poor region with some of the poorest nations in the Western hemisphere. The cases in this report were performed by advanced laparoscopic surgeons with the assistance of the FreeHand robot (Freehand 2010 Ltd., Guildford, Surrey, United Kingdom). This was a single robotic arm that controlled the laparoscope and was under the direct control of the surgeon *via* an infrared communicator. The resource poor nations in the Caribbean could not afford more advanced robotic platforms that are available on the commercial market, but we found this system to be a good intermediary that brought advantages over conventional laparoscopy while balancing cost.

In our small series, these operations were performed by advanced laparoscopic surgeons who were already facile with laparoscopic colectomies. Therefore, it was not surprising that the mean operating time was comparable to those in published reports on laparoscopic colectomies from the Caribbean[10, 11,16] that ranged from 150 min[10] to 175 min[16], as well as reports from international literature[17-20]. Similarly, our other outcomes were comparable to those in reports on laparoscopic colectomies from the region, where the median length of hospitalization ranged from 4[11] to 5[10] days, overall morbidity from 10%[10] to 35.3%[16] and no reported mortality[10,11,16].

Ballantyne *et al*[21] wrote during their early experience with robotic colectomies in 2001 that the DaVinci system overcame the pitfalls of conventional laparoscopy that included: an unstable video camera platform, limited motion (degrees of freedom) of straight laparoscopic instruments, two-dimensional imaging and poor surgeon ergonomics. Ballantyne *et al*[21] also wrote that "*inexperienced or bored camera-holders move the camera frequently and rotate it away from the horizon.*" We agree with Ballantyne *et al*[21] and we found that the surgeon being in full control of the visual field was a distinct advantage of the FreeHand robot. The operators also unanimously found the stability of the vision advantageous. In our cases, the robot was assigned a conventional 30-degree laparoscope with a single lens. Therefore, unlike the advanced multi-lens cameras in advanced robotic systems that allow depth perception, the FreeHand robot could not overcome the two-dimensional views that is a recognized limitation of conventional laparoscopy.

Surgeon ergonomics has been one criticism of the FreeHand platform. More sophisticated robotic systems such as the DaVinci platform would allow intra-corporeal articulation with specialized instruments, but the Freehand robot had only one arm to operate the camera. Therefore, conventional laparoscopic instruments had to be used in these cases. The straight, long instruments would still be limited in their motion by the fixation enforced by the abdominal wall trocars[21]. Providing more degrees of freedom of movement would require a more sophisticated robot with additional operating arms, but the point was already made that these come at a significant increase in cost. On the other

hand, all surgeons in our series unanimously reported that the robotic arm was not intrusive and did not negatively impact surgeon ergonomics, although it did not improve ergonomics either.

We have shown that the use of the FreeHand robot for laparoscopic colorectal resections is feasible, provides some advantages over conventional laparoscopy and has similar short-term outcomes to conventional laparoscopy. From this study, we cannot comment on the long-term outcomes, although we expect it to be similar conventional laparoscopy. It has already been proven and accepted from randomized controlled trials[2-7] and large metanalyses[7,8,22] that conventional laparoscopic colorectal resections have equivalent oncologic outcomes to open surgery.

LIMITATIONS

We acknowledge that these colorectal operations were performed by experienced surgeons who were already facile with laparoscopic colectomies and beyond the learning curves. Therefore, this does introduce some bias in outcomes, but it was equally important to show that this technique was feasible in this setting.

We also acknowledge that the sample size is small. This is a low resource nation with a population of 1.3 million persons so few persons qualified for use of the robotic arm during the study period.

CONCLUSION

We have shown that robot assisted colorectal surgery is feasible and safe in the resource-poor Caribbean setting.

ARTICLE HIGHLIGHTS

Research background

Laparoscopic colorectal surgery is still developing in the Anglophone Caribbean and there has been no report of robot assisted colorectal surgery in the region. This paper reports our initial experience with advanced colorectal surgery using the Freehand robot.

Research motivation

Robot-assisted colorectal surgery using the FreeHand® robotic camera holder (Freehand 2010 Ltd., Guildford, Surrey, United Kingdom) was introduced to the Caribbean in 2021. We report our initial experience with this technology.

Research objectives

This paper reports the initial experience with the FreeHand(R) robotic camera holder to complete colorectal operations in a resource-poor setting.

Research methods

A retrospective study was performed, collecting data from all consecutive patients who underwent colorectal operations using the FreeHand robot from September 2020 to April 2022. The data collected included: demographics, docking time, operating time, conversions, number and duration of intra-operative lens cleaning. All operating surgeons completed a survey that sought information on robot use.

Research results

There were 9 patients in this study who underwent: Right hemicolectomies (5), left hemicolectomy (1), sigmoid colectomies (2) and anterior resection (1). These operations were completed with a mean robot docking time of 6.33 min, mean duration of surgery of 122.33 min and mean estimated blood loss of 113.33 mL. The laparoscope was detached from the robot an average of 2.6 times per case, with cumulative mean interruption time of 4.2 min per case. The mean duration of hospitalization was 3.2 d and there were no complications recorded. Surgeons reported that there were good ergonomics, with no limitation on instrument movement, stable image and better control of surgical field.

Research conclusions

Robot-assisted laparoscopic colorectal surgery is feasible and safe in the resource-poor Caribbean setting, once there is appropriate training.

Research perspectives

Future research should incorporate large numbers of patients and a comparison of outcomes between robot-assisted and laparoscopic cases.

FOOTNOTES

Author contributions: Cawich SO wrote the paper and reviewed the paper for scientific accuracy; Naraynsingh V and Singh Y collected data and reviewed the manuscript for accuracy; Sensai R and Arulampalam T analyzed data and reviewed the manuscript for scientific accuracy.

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Country/Territory of origin: Trinidad and Tobago

ORCID number: Shamir O Cawich 0000-0003-3377-0303; Yardesh Singh 0000-0001-6058-6267; Vijay Naraynsingh 0000-0002-5445-3385; Ramdas Senasi 0000-0001-9894-877X; Tan Arulampalam 0000-0002-1784-7713.

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Rare case of perforated giant gastric ulcer with concurrent thyroid storm: A case report

Jasper Xiangwei Wang, Lin Seong Soh, Dinesh Carl Junis Mahendran, Chang Yi Woon, Clement Luck Khng Chia

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Jasper Xiangwei Wang, Lin Seong Soh, Clement Luck Khng Chia, Department of General Surgery, Khoo Teck Puat Hospital, Singapore 768828, Singapore

Dinesh Carl Junis Mahendran, Department of Endocrinology, Khoo Teck Puat Hospital, Singapore 768828, Singapore

Chang Yi Woon, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117597, Singapore

Corresponding author: Chang Yi Woon, MD, Doctor, Yong Loo Lin School of Medicine, National University of Singapore, 10 Medical Dr, Singapore 117597, Singapore 117597, Singapore. e0345822@u.nus.edu

Abstract

BACKGROUND

Thyroid storm is an uncommon condition manifesting in severe thyrotoxicosis with a high mortality rate. The concurrence of peptic ulcer disease and hyperthyroidism is rare due to concurrent activation of both the sympathetic and parasympathetic pathways. We present a case of perforated giant gastric ulcer with concurrent thyroid storm who underwent damage control surgery with emergency patch repair with falciform ligament and recovered well.

CASE SUMMARY

A 53-year-old male chronic smoker, with no previous medical history, presented with severe generalized abdominal pain and vomiting for one day duration. Further history revealed weight loss, diarrhea, and anxiety over the past three months. On clinical examination, patient was febrile with temperature of 38.6 Degrees Celsius and tachycardic at 130-140 beats per minute, his blood pressure was low at 90/50mmHg. His abdomen was tender with generalized peritonism. In view of his clinical history, a thyroid screen was ordered which showed raised thyroxine (T4) levels of 90.3 pmol/L and low thyroxine stimulating hormone (TSH) levels of 0.005 μ U/mL. Chest X-ray showed no sub-diaphragmatic free air, but contrasted CT scan revealed pneumoperitoneum with large amount of intraabdominal free fluid. The working diagnosis was perforated peptic ulcer complicated by thyroid storm. An urgent endocrinologist consult was made, and patient was started on beta blocker and intravenous steroids pre-operatively. The patient underwent emergency laparotomy with washout and patch repair of the

perforated gastric ulcer. Patient was monitored post-operatively in intensive care unit and required IV hydrocortisone and Lugol's iodine. Histology of the ulcer edges showed no malignancy. On post-operative day seven, T4 decreased to 20.4 pmol/L, TSH was 0.005 mLU/L. His thyroid function test subsequently normalized 3 mo post-operatively with T4 18.1 pmol/L, TSH 1.91 mLU/L. Patient's recovery was otherwise uneventful. Thyroid receptor antibody subsequently was positive, and patient was managed for Grave's disease by the endocrinologist.

CONCLUSION

This case highlights the rare but life-threatening clinical emergency of peptic ulcer perforation complicated by thyroid storm. Multidisciplinary perioperative management is crucial to optimize patient for surgery and damage control principles should be taken for an acute surgical patient with concurrent endocrine crisis.

Key Words: Peptic ulcer; Perforated viscus; Thyroid storm; Multidisciplinary; Grave's disease; Case report

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Core Tip: Concurrent peptic ulcer perforation and thyroid storm is a rare but life-threatening surgical emergency. Multidisciplinary perioperative management is crucial to optimize patient for surgery, and damage control principles should be taken for an acute surgical patient with concurrent endocrine crisis.

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INTRODUCTION

Thyroid storm is an acute, life-threatening, hypermetabolic state manifesting in severe thyrotoxicosis. This condition is uncommon and associated with a high mortality rate. The concurrence of peptic ulcer disease and hyperthyroidism is rare and the association between these two conditions is unusual. Few reports of perforated peptic ulcer complicated by thyroid storm have been reported, and these patients underwent trial of conservative management to optimize thyroid status before some required delayed surgical repair to control sepsis. We present a patient with perforated giant gastric ulcer with concurrent thyroid storm who was peritonitic and underwent damage control surgery with patch repair with falciform ligament and recovered uneventfully.

CASE PRESENTATION

Chief complaints

A 53-year-old male chronic smoker, with no past medical history presented to the emergency department with severe generalized abdominal pain and vomiting for one day duration.

History of present illness

Patient's symptoms started acutely one day ago. A history of weight loss, diarrhea and, anxiety over the preceding three months was also elicited from the patient.

History of past illness

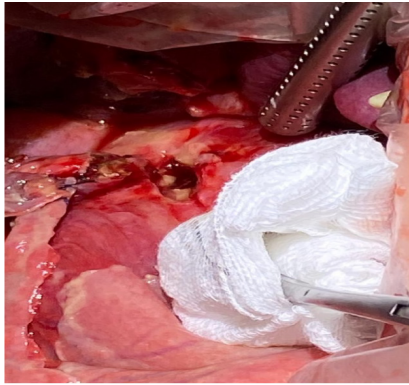
The patient had no past medical history.

Personal and family history

The patient had no significant personal and family history.

Physical examination

Clinically, patient was febrile with temperature of 38.6 Degrees Celsius and tachycardic at 130-140 beats per minute, blood pressure was 90/50 mmHg. On examination, his abdomen was tender with generalized peritonism. There was no goiter.



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Figure 1 Intraoperative picture of perforated giant gastric ulcer.

Laboratory examinations

A thyroid screen was performed in view of patient's history, which revealed a markedly raised thyroxine (T4) levels (90.3 pmol/L) and low levels of thyroid stimulating hormone (TSH) (0.005 μ U/mL) that suggested primary hyperthyroidism.

Imaging examinations

Chest X-ray showed no sub-diaphragmatic free air. A contrasted CT scan was performed and revealed pneumoperitoneum with large amount of intraabdominal free fluid.

MULTIDISCIPLINARY EXPERT CONSULTATION

In view of the suspicion of a concurrent acute thyroid storm in this patient with perforated viscus, a multidisciplinary consult was made with endocrinologist and pharmacist and patient was started on beta blocker and intravenous steroids pre-operatively.

FINAL DIAGNOSIS

The patient underwent emergency laparotomy, and a perforated giant gastric ulcer was found.

TREATMENT

Patient was optimized pre-operatively with beta blocker and intravenous steroids pre-operatively. Intra-operatively, there was gross soilage with a perforated 2.5cm gastric antral ulcer (Figure 1). Damage control surgery was performed, comprising washout and patch repair using a tongue of falciform ligament. Post-operatively, he required IV hydrocortisone and Lugol's iodine with monitoring in intensive care unit (ICU). Hydrocortisone was weaned off after 48 h and patient was started on propylthiouracil (PTU) with sips of water. Feeds were commenced after 3 days and PTU was subsequently changed to oral carbimazole (30 mg/d) on discharge. On post-operative day seven, T4 decreased to 20.4 pmol/L, TSH was 0.005 mLU/L. His thyroid function test subsequently normalized 3 mo post-operatively with T4 at 18.1 pmol/L, TSH 1.91 mLU/L. Ulcer edge histopathology showed organizing fibrosis with no malignancy. Thyroid receptor antibody returned as positive, and he was managed by the endocrinologist for Grave's disease.

OUTCOME AND FOLLOW-UP

The patient had an uneventful postoperative clinical course and was discharged one week post-operatively. He is on follow-up with the endocrinologist for Grave's disease in the outpatient clinic.

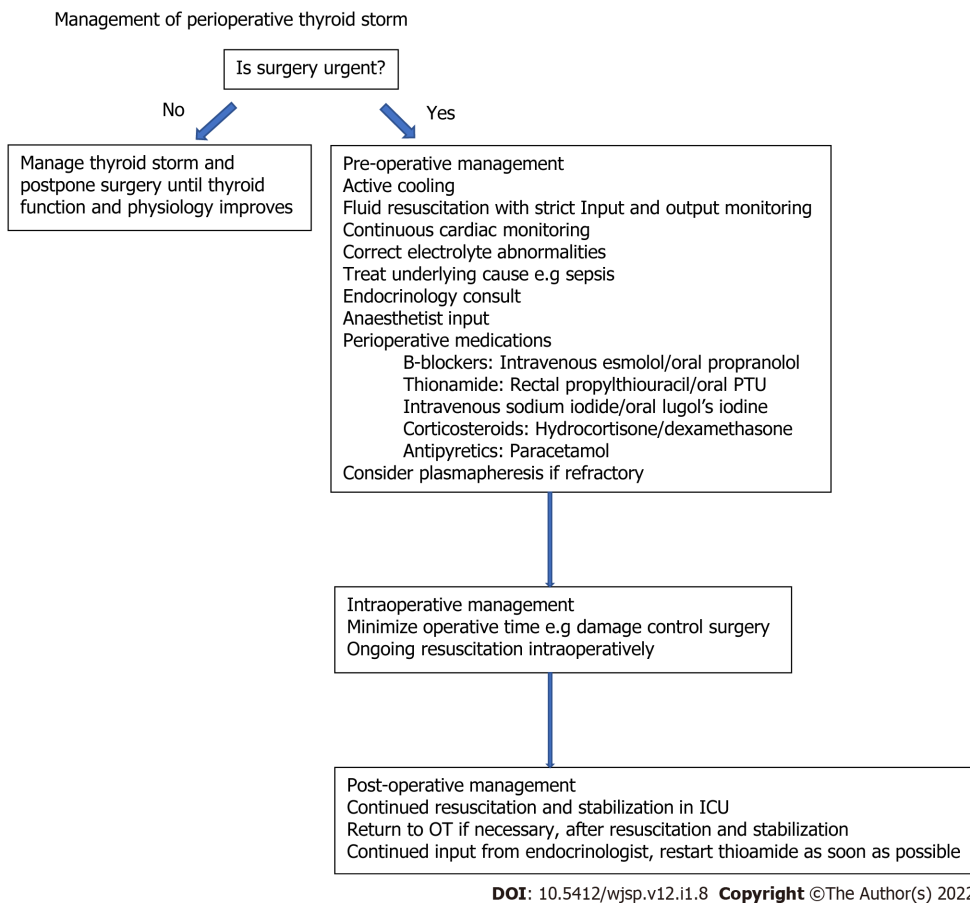


Figure 2 Perioperative management of patient with thyroid storm. PTU: Propylthiouracil; OT: Operating theatre; ICU: Intensive care unit.

DISCUSSION

Although causes for peptic ulcer disease (PUD) are well described, the association between hyperthyroidism and PUD is unusual due to differences in the autonomic activity behind these two disorders. PUD exhibits a parasympathetic predominance whereas sympathetic activity predominates in hyperthyroidism[1] with Ebert *et al*[2] showing that acid secretion is reduced in hyperthyroidism. These findings underscore the rarity of concurrent PUD with hyperthyroidism.

There are 3 cases of perforated peptic ulcer[3-5] complicated by thyroid storm reported in literature. All were treated conservatively till thyroid function improved prior to ulcer repair. While the Burch-Wartofsky score is routinely used as a diagnostic tool for thyroid storm, we note that there are conflicting factors in its calculation due to concurrent sepsis driving tachycardia and fever. However, the clinical history with markedly elevated T4 Levels and suppressed TSH levels suggested underlying untreated hyperthyroidism rather than an acute stress response.

Our patient was clinically septic and had generalized peritonism. IV beta-blockers and steroids were for rapid control of metabolic effects of thyrotoxicosis. Oral PTU was not used as in view of the perforation and requirements to be fasted. The alternative is rectal PTU prepared by the in-house pharmacist, but this requires 3-4 h of lead time. PTU takes days to manifest its anti-thyroid effects. Due to sepsis and peritonism, medical therapy and delay to further optimize him was inappropriate. Therefore, decision was made for emergency laparotomy.

Options for a giant gastric ulcer (defined as ulcer diameter > 2 cm) can be broadly divided into primary repair or resection surgery. The principles of damage control surgery in a severely physiologically challenged patient are central to the decision regarding the type of surgery. The aim is expeditious control of contamination and bringing the patient back to ICU for further resuscitation and restoration of physiology. Hence, a patch repair was chosen instead of a prolonged major resection. However, the lack of omentum in this thin patient made a patch repair challenging. As such an alternative using the falciform ligament which lies across the first part of the duodenum was chosen and easily mobilized for a tension-free patch repair. This case also highlights the utility of falciform ligament pedicle flap[6] as an alternative approach to repair perforated giant gastric ulcers and an attempt should be made to preserve the falciform ligament as a backup during initial midline laparotomy for a perforated viscus rather than routinely ligating and dividing it. Another alternative option to a damage control patch repair for large gastric ulcer perforation would be an ulcerectomy with/without pyloro-

plasty if a patch repair is deemed insufficient.

Postoperatively, the patient was transferred to ICU. The key principles of post-operative critical care management in this patient include aggressive resuscitation with fluids and empirical antibiotics, correction of thyroid dysfunction and nutritional support. Multidisciplinary collaboration involving the surgeon, intensivist and endocrinologist is key to good outcomes in an acute surgical patient with concurrent thyroid storm. A flowchart illustrating the principles of management is summarized in [Figure 2](#).

CONCLUSION

Concurrent peptic ulcer perforation with thyroid storm is a rare but life-threatening surgical emergency. Multidisciplinary perioperative management and damage control surgery are critical to control sepsis, restore physiology and correct thyroid dysfunction in an expeditious fashion.

FOOTNOTES

Author contributions: Wang JX, Soh LS, and Chia LKC were the patient's general surgeons, reviewed the literature and contributed to manuscript drafting; Mahendran D performed the endocrinological consult for the patient, reviewed the literature, and contributed to manuscript drafting; Woon CY was responsible for the revision of the manuscript; all authors issued final approval for the version to be submitted.

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Country/Territory of origin: Singapore

ORCID number: Jasper Xiangwei Wang 0000-0002-8115-0945; Lin Seong Soh 0000-0003-2872-6914; Dinesh Carl Junis Mahendran 0000-0001-8598-6961; Chang Yi Woon 0000-0001-6730-6774; Clement Luck Khng Chia 0000-0003-2248-9348.

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