Stevens Sean (Orcid ID: 0000-0003-3522-1412)
Wong Enoch (Orcid ID: 0000-0002-2983-4768)
Liu David S (Orcid ID: 0000-0001-8936-4123)

Title: Preoperative and intraoperative chemical thromboprophylaxis increases bleeding risk following elective cholecystectomy: a multicentre (PROTECTinG) study

Running title: Chemoprophylaxis timing in cholecystectomy

Authors

David S Liu (*PhD, FRACS*),^{1, 2, 7} Sean Stevens (*MSurgEd, FRACS*),^{1,4} Enoch Wong (*MBBS, FRACS*),³ Jonathan Fong (*MBBS, FRACS*),¹ Krinal Mori (*MS, FRACS*),^{1, 2, 5} Salena Ward (*MS, FRACS*),^{3, 6} Sharon Lee (*BBioMed, MD*),² Tess Howard (*MD*),¹ Anshini Jain (*MBBS, FRACS*),³ Anna Sonia Gill (*MBBS*),¹ Pith Soh Beh (*MBBS*),² Maeve Slevin (*MBChB*),² Wael Jamel (*MBChB*),¹ Nicola Fleming (*MD*),¹ Simon Bennet (*MBBS*),¹ Chi Chung (*MD*),³ Amy Crowe (*MD*),³ Vijayaragavan Muralidharan (*PhD, FRACS*),^{1,4} on behalf of the VERITAS collaborative.¹

Affiliations

1. Department of Surgery, Austin Health, 145 Studley Road, Heidelberg, Victoria, 3084
2. Department of Surgery, Northern Health, 185 Cooper Street, Epping, Victoria, 3076
3. Department of Surgery, Box Hill Hospital, 8 Arnold Street, Box Hill, Victoria, 3128
4. The University of Melbourne Department of Surgery, Austin Health, 145 Studley Road, Heidelberg, Victoria, 3084
5. The University of Melbourne Department of Surgery, Northern Health, 185 Cooper Street, Epping, Victoria, 3076
6. Monash University Eastern Health Clinical School, Box Hill, Victoria, 3128
7. Department of Surgery and Perioperative Medicine, Flinders Medical Centre, Flinders Drive, Bedford Park, South Australia, 5042

Corresponding author

David S Liu

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/ans.15998](https://doi.org/10.1111/ans.15998)

Flinders Medical Centre, Flinders Drive, Bedford Park, South Australia, 5042

Phone: +61 08 8204 5511

Email: liu.davidsh@gmail.com

Figures: 1

Tables: 2 main, 2 supplementary

Word count: 3999 including abstract, main text, references, tables and figures

Abstract

Background

Cholecystectomy is commonly performed in general surgery. Despite guidelines recommending chemical thromboprophylaxis in the perioperative period, the most appropriate time for its initiation is unknown. Here, we investigated whether timing of chemoprophylaxis affected venous thromboembolism (VTE) and bleeding rates post-cholecystectomy.

Methods

Retrospective review of all elective cholecystectomies performed between January 1, 2018 to June 30 2019, across 7 Victorian hospitals. Clinical VTE was defined as imaging-proven symptomatic disease within 30 days of surgery. Major bleeding was defined as the need for blood transfusion, surgical intervention, or >20 g/L fall in haemoglobin from baseline.

Results

1744 cases were reviewed. Chemoprophylaxis was given early (pre- or intra-operatively), postoperatively or not given in 847 (48.6%), 573 (32.9%), and 324 (18.6%) patients respectively. This varied significantly between surgeons, fellows, trainees and institutions. Clinical VTE occurred in 5 (0.3%) patients and was not associated with chemoprophylaxis timing. Bleeding occurred in 42 (2.4%) patients. Of this, half were major events, requiring surgical control in 5 (11.9%) patients and blood transfusion in 9 (21.4%) patients. Bleeding also extended length of stay (mean (SD), 3.1 (4.0) vs 1.4 (2.2) days, $p < 0.001$). One bleeding-related mortality was recorded. Importantly, when compared with postoperative (RR 1.46, 95% CI 1.21-1.62) and no (RR 1.23, 95% CI 1.03-1.35) chemoprophylaxis, early usage significantly increased bleeding risk and independently predicted its occurrence.

Conclusions

Perioperative chemoprophylaxis is variable among patients undergoing elective cholecystectomy. The rate of clinical VTE post-cholecystectomy is low. Early chemoprophylaxis increases bleeding risk without an appreciable additional protection from VTE.

Key words

General surgery, cholecystectomy, thromboembolism, prophylaxis, timing,

Introduction

Venous thromboembolism (VTE), which incorporates deep vein thrombosis (DVT) and pulmonary embolism (PE), is recognised by the Australian Commission on Safety and Quality in Healthcare as a major hospital-acquired complication, accounting for 10% of all preventable hospital-related mortalities (1). General surgical patients, particularly those who undergo major laparoscopic surgeries, are at risk of VTE (2). Proven mechanical and chemical preventative strategies are being employed to minimise the morbidity and healthcare costs associated with hospital-acquired VTE (3-6). However, thromboprophylaxis is not risk free. In particular, chemoprophylaxis carries a 2-3% risk of bleeding (7). Therefore, appropriate chemoprophylaxis prescription requires balancing the risk of bleeding with thromboembolic protection.

Regulatory bodies, including the Royal Australasian College of Surgeons, have released guidelines for the usage of thromboprophylaxis (8). Despite its common practice and the significant body of research on this topic, controversies still surround when to initiate chemoprophylaxis in the perioperative period. Traditionally, chemoprophylaxis has been administered pre- or intra-operatively, with the aim of mitigating the potential risk of thromboembolism that occurs as a consequence of the physiological disturbances during surgery (9, 10). Interestingly, the risk of developing 'on-table' VTE has never been proven. Furthermore, the practice of preoperative chemoprophylaxis stems from early clinical trials which compared chemoprophylaxis given two hours before knife-to-skin to placebo, in the absence of mechanical thromboprophylaxis (3, 4). In contrast, there is increasing evidence from patients undergoing elective and emergency orthopaedic surgeries that preoperative chemoprophylaxis increases bleeding complications without

reducing VTE rates when compared with postoperative chemoprophylaxis (11, 12). In light of these findings, the timing of chemoprophylaxis for patients undergoing general surgical operations deserve further investigation.

Cholecystectomy is one of the most commonly performed major general surgical operations. The lack of evidence to inform optimal timing of perioperative chemoprophylaxis, complicated by the potential risk of increased bleeding, has anecdotally contributed to heterogeneity in clinical practice amongst general surgeons when performing this surgery. To address this issue, the VERITAS (Victorian-collaborative for Education, Research, Innovation, Training and Audit by Surgical trainees) collaborative has established the PROTECTinG (Perioperative Timing of Elective Chemical Thromboprophylaxis in General surgery) trial. In this study, we describe the variability in perioperative chemoprophylaxis among patients undergoing elective cholecystectomies. Importantly, we also investigate whether the timing of chemoprophylaxis affects the rate of bleeding and symptomatic VTE post-cholecystectomy.

Methods

Study design

A retrospective review was performed for consecutive patients who underwent elective cholecystectomy from 1 January 2018 to 30 June 2019 at seven Victorian hospitals in Australia. These hospitals are incorporated into three health networks including Austin Health (Austin Hospital, Heidelberg Repatriation Hospital), Northern Health (The Northern Hospital, Broadmeadows Hospital), and Eastern Health (Box Hill Hospital, Maroondah Hospital, Angliss Hospital). Overall, surgeries were performed by 86 consultant surgeons, 16 surgical fellows and 71 trainees. Patients were identified from each hospital's administrative database using the Australian Classification of Health Interventions procedural code for cholecystectomy (30443, 30445). We excluded patients under 18 years of age, emergency surgery, and where cholecystectomy was not the primary procedure. This study received ethics approval across all three health networks (35678).

VTE prophylaxis

The type and timing of thromboprophylaxis was at the discretion of the treating surgeon. Mechanical thromboprophylaxis included graduated compression stockings (GCSs) and sequential compression devices (SCDs) used either in combination or in isolation. Chemoprophylaxis was administered using either enoxaparin (daily), dalteparin (daily) or heparin (twice daily), delivered subcutaneously, at doses adjusted to each patient's weight and renal function. The timing of chemoprophylaxis was classified into three groups: administered early (pre- or intra-operatively), postoperatively (following skin closure) or not given at all.

Data collection

Data was extracted from patient records onto a universal electronic proforma. This included demographics, medical co-morbidities, ASA score at time of surgery, risk factors for VTE and bleeding, anaesthetic and operative details, timing and type of thromboprophylaxis, perioperative investigations, as well as postoperative bleeding and VTE events. As multiple investigators were responsible for data collection, standardised training sessions were conducted prior to study commencement to minimise interobserver disagreements.

Study endpoints and definitions

The primary endpoint of this study is the rate of postoperative bleeding. Secondary endpoints include length-of-hospital stay as well as 30-day clinical VTE and mortality rates. Postoperative bleeding was defined as bleeding that occurred within the same admission period following surgery. Major bleeding was defined as the need for blood transfusion, surgical intervention, or >20 g/L fall in haemoglobin from baseline (11). Clinical VTE was defined as imaging-proven (CT pulmonary angiography, V/Q scan or venous duplex ultrasound) symptomatic disease within 30 days of surgery. In patients who used dual anti-platelet agents preoperatively, the non-aspirin medication was ceased seven days prior to cholecystectomy. In patients who were therapeutically anticoagulated preoperatively, bridging enoxaparin was stopped 24 hr prior to cholecystectomy. All patients were routinely followed up in clinic between four to six weeks post discharge.

Statistical analysis

A power calculation was performed based on a 3% bleeding risk following elective cholecystectomy (7). We considered an absolute difference of 2% between study groups to be clinically significant. The calculated sample size required per group was 430 cases to achieve 80% statistical power ($\alpha < 0.05$). Continuous and categorical variables were analysed with the Student's *t*-test and Chi-square test, respectively. To determine independent predictors of postoperative bleeding, a multivariate analysis using a backward stepwise regression algorithm was subsequently performed, based on parameters found statistically significant on univariate analysis. A two-tailed $p < 0.05$ and 95% confidence interval (CI) around the odds ratio (OR) or risk ratio (RR) that did not cross one was considered statistically significant. Statistical analyses were conducted using Prism v8 (GraphPad Software) and SPSS v24 (IBM).

Results

Variability in chemoprophylaxis among patients undergoing cholecystectomy

In total, 1744 patients underwent elective cholecystectomy (laparoscopic 99.0%, open 1.0%) for symptomatic cholelithiasis. Chemoprophylaxis was given early, postoperatively or not given in 847 (48.6%), 573 (32.9%), and 324 (18.6%) patients respectively (**Fig 1a**). Overall, 1043 (59.8%) patients received one prophylactic dose of anticoagulant, whilst two or more doses were given to 377 (21.6%) patients. Moreover, 29.2% of patients in the early chemoprophylaxis group and 22.7% of patients in the postoperative chemoprophylaxis group received ≥ 2 doses of anticoagulant in the perioperative period. For those who only received postoperative chemoprophylaxis, the median time from completion of surgery to anticoagulant administration was 10.2 hr (IQR 7.7-19.9 hr). Notably, the timing and use of chemoprophylaxis varied significantly between health networks (**Fig 1b**) and surgeon seniority (**Fig 1c**). In contrast, intraoperative mechanical thromboprophylaxis was utilised in 1670 (95.8%) patients. Of these, combination SCDs and GCSs were applied in 1176 (67.4%) patients, while GCSs or SCDs were solely prescribed in 428 (24.5%) and 66 (3.8%) patients respectively.

Factors associated with the use and timing of perioperative chemoprophylaxis

Following univariate analysis, the factors that were significantly associated with the use of chemoprophylaxis included older age, higher ASA score, longer operative time, greater VTE risk (based on Caprini score (13)), pre-existing use of therapeutic anticoagulation, and higher baseline bilirubin levels (**Table S1**). To explore this further, we found that older age, male gender, pre-existing therapeutic anticoagulation, higher baseline creatinine and lower bilirubin levels were associated with postoperative rather than early use of chemoprophylaxis (**Table S2**).

The incidence of clinical thromboembolism following cholecystectomy

In total, four DVTs and one PE were identified, resulting in an overall 30-day clinical VTE rate of 0.3% post cholecystectomy. These events occurred in patients with a Caprini score of ≥ 3 (moderate and high VTE risk). Interestingly, all VTE cases appeared in those who received chemoprophylaxis. However, the rate of clinical VTE was not significantly different when compared to patients who did not receive chemoprophylaxis (0.3% vs 0.0%, RR 1.23,

95% CI 0.63-5.03, $p=1.000$). Of the five VTE cases, four had early chemoprophylaxis. There was no significant difference between early and postoperative chemoprophylaxis groups in their incidence of clinical VTE (0.4% vs 0.2%, RR 1.34, 95% CI 0.63-1.63, $p=0.654$).

Early chemoprophylaxis is associated with an increased risk of bleeding following cholecystectomy

Bleeding occurred in 42 (2.4%) patients, of which 21 (1.2%) cases were major events. Haemoperitoneum (50.0%), wound haematoma (45.2%), rectus sheath haematoma (2.4%) and haematuria (2.4%) accounted for all cases of bleeding. Surgical haemostasis was required in five (11.9%) patients while the remaining cases responded to ward-based interventions. Nine (21.4%) patients received blood transfusions. Compared with non-bleeders, bleeding extended length-of-stay (mean (SD), 3.1 (4.0) vs 1.4 (2.2) days, $p<0.001$). One (0.06%) bleeding-related mortality was recorded.

Importantly, when compared with postoperative (RR 1.36, 95% CI 1.01-1.57, $p=0.046$) and no (RR 1.39, 95% CI 1.13-11.53, $p=0.005$) chemoprophylaxis, early usage significantly increased the risk of major bleeding following cholecystectomy (**Table 1**). In contrast, this risk was comparable between the postoperative and no chemoprophylaxis groups (RR 1.57, 95% CI 0.80-3.30, $p=0.303$). Based on univariate analysis, the factors that were significantly associated with postoperative bleeding include male gender, increasing age, higher Caprini and ASA scores, longer surgical time, consultant surgeon as the primary operator, pre- and postoperative anticoagulant use, lower baseline platelet count, higher preoperative bilirubin level, repeated chemoprophylaxis usage and early chemoprophylaxis administration (**Table 2**). Of these, male gender (OR 2.68, 95% CI 1.23-5.84, $p=0.013$), postoperative therapeutic anticoagulation (OR 5.29, 95% CI 1.58-17.67, $p=0.007$) and early chemoprophylaxis (OR 4.88, 95% CI 1.65-14.45, $p=0.004$) were independent predictors of bleeding following elective cholecystectomy.

Discussion

This is the first study to examine whether timing of chemoprophylaxis affects the rate of bleeding and VTE following elective cholecystectomy. The key findings were significantly higher rates of bleeding when chemoprophylaxis was initiated during or prior to surgery without an apparent benefit in VTE prevention. This is in the context of a low incidence of symptomatic VTE post cholecystectomy. Furthermore, this multicentre study highlights the heterogeneity that exist between consultants, surgical fellows, trainees and health networks with respect to the practice of thromboprophylaxis in the perioperative period.

The rates of symptomatic VTE (0.3%) and postoperative bleeding (2.4%) in our cohort are comparable to international studies (14-23). Importantly, our findings reflect those seen in patients who have undergone hip arthroplasty and spinal surgery (11, 12), that when compared with early chemoprophylaxis, its postoperative use is associated with a lower risk of bleeding without compromising protection against thromboembolism.

Fundamentally, perioperative chemoprophylaxis requires balancing the risk of bleeding and thromboembolism. Although many clinicians are dogmatic about initiating pre- or intra-operative chemoprophylaxis, there is in fact minimal evidence to directly support this practice. The use of early chemoprophylaxis has been largely driven by three notions; 1) initial clinical trials which demonstrated that preoperative unfractionated or low molecular weight heparin decreased the rate of thromboembolism in general surgical patients (3, 4), 2) a hypothesis that laparoscopic surgery promotes lower limb venous stasis due to intrabdominal pressurisation in a paralysed patient (9, 10), and 3) a global effort to promote the use of thromboprophylaxis in order to minimise a potentially preventable hospital-acquired complication (1). However, it is worth noting that these early clinical trials did not include a postoperative chemoprophylaxis group. They were also conducted in the absence of mechanical thromboprophylaxis, which now has proven anti-thrombotic efficacy (5). Furthermore, despite changes in venous circulation during laparoscopic surgery (9, 10), this has never been conclusively shown to precipitate thrombosis. Additionally, with continued advances in surgical techniques and technologies, operations like cholecystectomy has significantly shortened in duration (24), thus reducing any potential risks conferred by physiological changes during surgery. In contrast, prophylactic doses of

anticoagulants carry an overall 2-4% risk of bleeding which incur patient morbidity and healthcare costs (7). Therefore, the ideal chemoprophylactic regimen is one that maximises thromboembolic protection whilst minimising bleeding risk. Towards this goal, our findings suggest that in patients undergoing elective cholecystectomy, postoperative chemoprophylaxis may mitigate the risk of anticoagulant-related bleeding whilst providing adequate protection against clinical VTE. Based on our data, the number needed to treat to prevent one case of clinical VTE is 345. In comparison, the number needed to harm secondary to major bleeding is 50 for early and 189 for postoperative chemoprophylaxis.

Our findings are clinically significant. This is particularly so, given the low risk of symptomatic VTE post elective cholecystectomy, the variability in chemoprophylactic practices amongst surgeons and the sheer number of cholecystectomies performed each year. In 2019, more than 50,000 cholecystectomies were undertaken in Australia (25). Therefore, a 1.3% absolute risk reduction in major postoperative bleeding potentially translates to >650 patients saved from bleeding-related morbidity and mortality per year.

Consistent with Kawamoto et al (19), our multivariate analysis also identified postoperative therapeutic anticoagulation and male gender as independent predictors for bleeding. Although their mechanistic basis is unclear, it is possible that early recommencement of therapeutic anticoagulation and the challenges associated with cholecystectomies in men may partially explain their risk profiles (26). Importantly, based on these findings, we caution against the use of early chemoprophylaxis in men and in those who intend to recommence therapeutic anticoagulation soon after surgery.

This study also highlights the significant variability in the use and timing of chemoprophylaxis among patients undergoing cholecystectomy. This finding is shared by other authors worldwide (18, 20, 27), and likely reflects poor evidence and a lack of consensus guidelines on this issue. Although we have identified key patient factors relating to the use and timing of chemoprophylaxis, we recognise that surgeon and institutional preferences may contribute to

heterogeneity in clinical practice. These aspects are being actively explored by the PROTECTinG investigators within the VERITAS collaborative.

The limitations of this study are inherent in its retrospective design. Firstly, correct interpretation of patient records was critical for data accuracy. We employed a range of strategies to minimise interobserver disagreements. These included the use of a universal data collection tool, standardised training sessions for data collectors, extracting parameters that were quantitative or binary in nature, and documented as part of routine care across the seven hospitals. Secondly, the incidence of bleeding and VTE may have been underestimated because each hospital's database does not capture diagnoses made external to their respective health network. Despite this, all bleeding episodes occurred within the index surgical admission, the diagnosis of major bleeding and symptomatic VTE were supported by biochemical or radiological investigations, all patients were adequately followed up, and our event rates are consistent with other studies. We acknowledge however, that the true incidence of VTE, including asymptomatic cases, could not be defined by this study.

To conclude, in patients undergoing elective cholecystectomy, the use and timing of perioperative chemoprophylaxis is highly variable. The rate of clinical VTE following cholecystectomy is low. Compared with postoperative chemoprophylaxis, initiation before or during surgery increases bleeding risk without an appreciable added protection from VTE. National standardisation of perioperative thromboprophylactic practices should be considered.

Disclosure statement

The authors have no conflicts of interest to declare

References

1. Australian Commission on Safety and Quality in Health Care. Venous thromboembolism prevention clinical care standard. [Cited 26 March 2020]. Available from: <https://www.safetyandquality.gov.au/our-work/clinical-care-standards/venous-thromboembolism-prevention-clinical-care-standard>
2. Ageno W, Dentali F, Squizzato A. Prophylaxis of venous thromboembolism following laparoscopic surgery: where is the evidence? *J Thromb Haemost*. 2005;3(2):214-5.
3. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med*. 1988;318(18):1162-73.
4. Mismetti P, Laporte S, Darmon JY, Buchmuller A, Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. *Br J Surg*. 2001;88(7):913-30.
5. Sachdeva A, Dalton M, Lees T. Graduated compression stockings for prevention of deep vein thrombosis. *Cochrane Database Syst Rev*. 2018;11:CD001484.
6. Kakkos SK, Caprini JA, Geroulakos G, Nicolaides AN, Stansby G, Reddy DJ, et al. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism. *Cochrane Database Syst Rev*. 2016;9:CD005258.
7. Leonardi MJ, McGory ML, Ko CY. The rate of bleeding complications after pharmacologic deep venous thrombosis prophylaxis: a systematic review of 33 randomized controlled trials. *Arch Surg*. 2006;141(8):790-7; discussion 7-9.
8. The Australian and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism. Prevention of venous thromboembolism, Best practice guidelines for Australia and New Zealand. Fourth Edition [PDF on Internet]. The Royal Australasian College of Surgeons. [Cited 28 March 2020]. Available from: https://umbraco.surgeons.org/media/1621/vte_guidelines.pdf
9. Jorgensen JO, Lalak NJ, North L, Hanel K, Hunt DR, Morris DL. Venous stasis during laparoscopic cholecystectomy. *Surg Laparosc Endosc*. 1994;4(2):128-33.

10. Sobolewski AP, Deshmukh RM, Brunson BL, McDevitt DT, VanWagenen TM, Lohr JM, et al. Venous hemodynamic changes during laparoscopic cholecystectomy. *J Laparoendosc Surg.* 1995;5(6):363-9.
11. Hull RD, Pineo GF, Francis C, Bergqvist D, Fellenius C, Soderberg K, et al. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients: a double-blind, randomized comparison. The North American Fragmin Trial Investigators. *Arch Intern Med.* 2000;160(14):2199-207.
12. Khan M, Jehan F, O'Keeffe T, Hamidi M, Truitt M, Zeeshan M, et al. Optimal Timing of Initiation of Thromboprophylaxis after Nonoperative Blunt Spinal Trauma: A Propensity-Matched Analysis. *J Am Coll Surg.* 2018;226(5):760-8.
13. Bahl V, Hu HM, Henke PK, Wakefield TW, Campbell DA, Jr., Caprini JA. A validation study of a retrospective venous thromboembolism risk scoring method. *Ann Surg.* 2010;251(2):344-50.
14. Henry ML, Abdul-Sultan A, Walker AJ, West J, Humes DJ. Duration and Magnitude of Postoperative Risk of Venous Thromboembolism after Cholecystectomy: A Population-Based Cohort Study. *Dig Surg.* 2020;37(1):32-8.
15. Ulrych J, Kvasnicka T, Fryba V, Komarc M, Malikova I, Burget F, et al. 28 day post-operative persisted hypercoagulability after surgery for benign diseases: a prospective cohort study. *BMC Surg.* 2016;16:16.
16. Stromberg J, Sadr-Azodi O, Videhult P, Hammarqvist F, Sandblom G. Incidence and risk factors for symptomatic venous thromboembolism following cholecystectomy. *Langenbecks Arch Surg.* 2015;400(4):463-9.
17. Rondelli F, Manina G, Agnelli G, Becattini C. Venous thromboembolism after laparoscopic cholecystectomy: clinical burden and prevention. *Surg Endosc.* 2013;27(6):1860-4.
18. Persson G, Stromberg J, Svennblad B, Sandblom G. Risk of bleeding associated with use of systemic thromboembolic prophylaxis during laparoscopic cholecystectomy. *Br J Surg.* 2012;99(7):979-86.
19. Kawamoto Y, Fujikawa T, Sakamoto Y, Emoto N, Takahashi R, Kawamura Y, et al. Effect of antithrombic therapy on bleeding complications in patients receiving emergency cholecystectomy for acute cholecystitis. *J Hepatobiliary Pancreat Sci.* 2018;25(11):518-26.
20. Gundogdu RH, Oduncu M, Bozkirli BO, Yazicioglu MO, Akbaba S. Does thromboprophylaxis cause bleeding after laparoscopic cholecystectomy? *Bratisl Lek Listy.* 2017;118(3):156-9.

21. Alizadeh RF, Sujatha-Bhaskar S, Li S, Stamos MJ, Nguyen NT. Venous thromboembolism in common laparoscopic abdominal surgical operations. *Am J Surg*. 2017;214(6):1127-32.
22. Stein PD, Matta F, Sabra MJ. Pulmonary embolism and deep venous thrombosis following laparoscopic cholecystectomy. *Clin Appl Thromb Hemost*. 2014;20(3):233-7.
23. Nguyen NT, Hinojosa MW, Fayad C, Varela E, Konyalian V, Stamos MJ, et al. Laparoscopic surgery is associated with a lower incidence of venous thromboembolism compared with open surgery. *Ann Surg*. 2007;246(6):1021-7.
24. Moore MJ, Bennett CL. The learning curve for laparoscopic cholecystectomy. The Southern Surgeons Club. *Am J Surg*. 1995;170(1):55-9.
25. Australian Commission on Safety and Quality in Health Care. Australian Atlas of Healthcare Variation Series 2019 [Cited 28 March 2020]. Available from: [https://www.safetyandquality.gov.au/publications-and-resources/australian-atlas-healthcare-variation-series#third-atlas-\(2018\)-by-topic](https://www.safetyandquality.gov.au/publications-and-resources/australian-atlas-healthcare-variation-series#third-atlas-(2018)-by-topic)
26. Inoue K, Ueno T, Douchi D, Shima K, Goto S, Takahashi M, et al. Risk factors for difficulty of laparoscopic cholecystectomy in grade II acute cholecystitis according to the Tokyo guidelines 2013. *BMC Surg*. 2017;17(1):114.
27. Lindberg F, Bjorck M, Rasmussen I, Bergqvist D. Current use of thromboembolism prophylaxis for laparoscopic cholecystectomy patients in Sweden. *Surg Endosc*. 2005;19(3):386-8.

Figures

Figure 1. (A) Perioperative use chemoprophylaxis in patients undergoing laparoscopic cholecystectomy across seven Victorian hospitals. The pattern of chemoprophylaxis utilisation between different health networks (B) and across surgeon seniorities (C).

Table 1. Bleeding following laparoscopic cholecystectomy

	Early prophylaxis N=847	Postop prophylaxis N=573	No prophylaxis N=324	Early vs Postop		Early vs No		Postop vs No	
				RR (95% CI)	p value	RR (95% CI)	p value	RR (95% CI)	p value
All	33	5	4	1.46		1.23		0.87	
bleeding, n (%)	(3.90)	(0.87)	(1.23)	(1.21-1.62)	<0.001	(1.03-1.35)	0.023	(0.41-1.28)	0.730
Major	17	4	0	1.36		1.39		1.57	
bleeding, n (%)	(2.01)	(0.70)	(0.00)	(1.01-1.57)	0.046	(1.13-11.53)	0.005	(0.80-3.30)	0.303
Minor	16	1	4	1.59		1.11		0.31	
bleeding, n (%)	(1.89)	(0.17)	(1.23)	(1.23-1.71)	0.002	(0.81-1.28)	0.615	(0.06-0.98)	0.060
Return to	3	2	0	1.01		1.38		1.57	
theatre, n (%)	(0.35)	(0.35)	(0.00)	(0.39-1.49)	1.000	(0.61-11.48)	0.565	(0.53-13.17)	0.538
Blood	7	2	0	1.31		1.39		1.57	
transfusion, n (%)	(0.83)	(0.35)	(0.00)	(0.76-1.59)	0.327	(0.89-11.49)	0.050	(0.53-13.17)	0.538
Hb drop,	-10	-8	-8						
g/L, median (IQR)	(-17, -4)	(-15, 0)	(-14, -0.5)	-	0.035	-	0.043	-	0.655

CI: confidence interval, Hb: haemoglobin, IQR: inter-quartile range, RR: risk ratio. Bold: highlight significance differences between groups.

Table 2. Predictors of postoperative bleeding

Parameters	Bleed N=42	No bleed N=1702	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p value	OR (95% CI)	p value
Gender, male, n (%)	21 (50.0)	508 (29.8)	2.35 (1.28-4.32)	0.005	2.68 (1.23-5.84)	0.013
Age, median (IQR)	59.3 (48.5, 77.0)	48.9 (37.0, 62.3)	-	<0.001	-	-
BMI, kg/m ² , mean (SD)	30.9 (6.9)	30.1 (8.0)	-	0.571	-	-
Caprini score, median (IQR)	5 (4, 6)	4 (3, 5)	-	<0.001	-	-
ASA score, median (IQR)	2 (2, 3)	2 (1, 2)	-	0.002	-	-
Surgery length, min, mean (SD)	109.1 (54.9)	84.1 (37.0)	-	<0.001	-	-
Laparoscopic approach, n (%)	41 (97.6)	1686 (99.1)	0.39 (0.06-4.20)	0.348	-	-
Consultant operator, n (%)	25 (59.5)	717 (42.1)	2.02 (1.10-3.71)	0.024	-	-
Benign pathology, n (%)	41 (97.6)	1694 (99.5)	0.19 (0.03-2.20)	0.088	-	-
Hospital network A, n (%)	15 (35.7)	383 (22.5)	1.91 (1.00-3.57)	0.067	-	-
<u>Preoperative</u>						
Therapeutic anticoagulant, n (%)	5 (11.9)	42 (2.5)	5.34 (2.17-13.88)	0.005	-	-
Anti-platelet agents, n (%)	7 (16.7)	138 (8.1)	2.27 (0.95-4.99)	0.079	-	-
Haemoglobin, g/L, mean (SD)	140.5 (22.0)	139.2 (14.0)	-	0.540	-	-
Platelet count, x10 ⁹ /L, mean (SD)	243.5 (62.0)	269.8 (74.5)	-	0.026	-	-
Creatinine, µmol/L, mean (SD)	76.4 (23.3)	70.3 (23.7)	-	0.114	-	-
INR, mean (SD)	1.0 (0.1)	1.0 (0.1)	-	0.161	-	-
Bilirubin, µmol/L, mean (SD)	23.6 (23.4)	16.1 (13.6)	-	0.001	-	-
<u>Postoperative</u>						
Therapeutic anticoagulant, n (%)	4 (9.5)	29 (1.7)	5.46 (2.07-13.12)	0.002	5.29 (1.58-17.67)	0.007
Anti-platelet agents, n (%)	7 (16.7)	126 (7.4)	2.50 (1.05-5.52)	0.052	-	-
<u>Chemoprophylaxis</u>						
Usage, yes, n (%)	38 (90.5)	1382 (81.2)	2.17 (0.82-5.81)	0.127	-	-
Repeated dosing, yes, n (%)	23 (54.8)	354 (20.8)	4.61 (2.53-8.73)	<0.001	-	-
Timing, early, n (%)	33 (78.6)	814 (47.8)	3.88 (1.90-7.95)	<0.001	4.88 (1.65-14.45)	0.004

ASA: American Society of Anaesthesiology, BMI: body mass index, CI: confidence interval, INR: international normalised ratio, IQR: interquartile range, OR: odds ratio, SD: standard deviation. Bold: highlight significance differences between groups.

ANS_15998_Fig1.jpg

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Liu, DS;Stevens, S;Wong, E;Fong, J;Mori, K;Ward, S;Lee, S;Howard, T;Jain, A;Gill, AS;Beh, PS;Slevin, M;Jamel, W;Fleming, N;Bennet, S;Chung, C;Crowe, A;Muralidharan, V

Title:

Pre-operative and intra-operative chemical thromboprophylaxis increases bleeding risk following elective cholecystectomy: a multicentre (PROTECTinG) study

Date:

2020-06-09

Citation:

Liu, D. S., Stevens, S., Wong, E., Fong, J., Mori, K., Ward, S., Lee, S., Howard, T., Jain, A., Gill, A. S., Beh, P. S., Slevin, M., Jamel, W., Fleming, N., Bennet, S., Chung, C., Crowe, A. & Muralidharan, V. (2020). Pre-operative and intra-operative chemical thromboprophylaxis increases bleeding risk following elective cholecystectomy: a multicentre (PROTECTinG) study. ANZ JOURNAL OF SURGERY, 90 (12), pp.2449-2455. <https://doi.org/10.1111/ans.15998>.

Persistent Link:

<http://hdl.handle.net/11343/275883>