

Research Idea

Ultrasound for the Diagnosis of Acute Calculous Cholecystitis, and the Impact of Analgesics: A Retrospective Cohort Study

Jason Friesen[‡], Brendon Friesen[§], Ee Syn Tan[|][‡] Medical student (MD). BSc. Royal Brisbane and Women's Hospital, University of Queensland, Brisbane, Australia[§] Radiologist. MBBS, BMedSc, FRANZCR. Lake Imaging, St. John of God, Geelong, Australia[|] General Surgical Registrar. MBBS, PGDipSurgAnat. Department of General Surgery, Monash Health, Dandenong, AustraliaCorresponding author: Jason Friesen (jason_friesen@live.com)

Reviewable v1

Received: 29 Jun 2018 | Published: 02 Jul 2018

Citation: Friesen J, Friesen B, Tan E (2018) Ultrasound for the Diagnosis of Acute Calculous Cholecystitis, and the Impact of Analgesics: A Retrospective Cohort Study. Research Ideas and Outcomes 4: e28069.

<https://doi.org/10.3897/rio.4.e28069>

Keywords

acute calculous cholecystitis ultrasound analgesia

Overview and background

Cholecystitis is inflammation of the gallbladder, with the commonest cause being gallstones (cholelithiasis). Gallstones are common, and are present in 25-30% of Australians over the age of 50 (Gastroenterological Society of Australia 2016) (however, in the US, only 1-3% of people with gallstones become symptomatic each year) (Heuman 2016). A gallstone may block drainage of the gallbladder by becoming lodged in the gallbladder neck or cystic duct. This blockage can result in colicky pain of the upper right quadrant or epigastrium, stasis of bile in the gallbladder and increased intraluminal pressure, leading to inflammation. The gallbladder also becomes distended which can compromise its lymphatic drainage and blood supply (NJ and G 2012). Cholecystitis secondary to cholelithiasis is called acute calculous cholecystitis.

Early, accurate diagnosis is important, as complications can arise. Such complications include; bacterial infection of the gallbladder, perforation, and emphysematous cholecystitis which involves gas in the gallbladder wall produced by certain infectious bacteria (NJ and G 2012). The standard treatment for cholecystitis is laparoscopic cholecystectomy, however if diagnosis is delayed resulting in a delayed cholecystectomy, complications may necessitate open surgery (Eldar et al. 1997, Peng et al. 2005, Madan et al. 2002)

The diagnostic tool of choice is ultrasound. It is more sensitive and specific than CT or MRI, and while some studies report greater diagnostic accuracy with cholescintigraphy (Shea 1994), ultrasound is still preferred due to clinician preference and cost (Pinto et al. 2013). Ultrasound also has the advantage of being able to elicit a “Sonographic Murphy Sign” (SMS) which is tenderness when the ultrasound probe is pressed on an inflamed gallbladder (and important sign of cholecystitis) (Bree 1995).

It is important to have an accurate imaging modality in acute calculous cholecystitis to ensure early intervention to prevent complications. It is also important to prevent unnecessary treatment in the event of a false positive finding (such as an invasive surgery). While the diagnostic specificity of ultrasound has reported to be as high as 95-99%, sensitivity values range from 84-97% (Shea 1994). There can be severe consequences to a false negative finding in someone who has acute calculous cholecystitis. Some reasons for a false negative, may be difficulties eliciting the SMS due to the patient's body habitus, a high intercostal position of the gallbladder fossa, obscuring bowel gas, and operator or diagnostic error. Many patients will go on to have emergency cholecystectomy despite a negative finding. This decision is often based on clinical suspicion and excluding other pathologies. After cholecystectomy, acute cholecystitis can then be confirmed by pathology via macroscopic and histological analysis, which is the gold standard for diagnosis.

On ultrasound, findings in acute calculous cholecystitis often include one or more of the following; impacted gallstone(s), gallbladder wall thickening (>3mm), a positive SMS, and secondarily; hyperaemia and pericholecystic fluid (Trowbridge et al. 2003, Nino-Murcia and Jeffrey 2001). Since gallstones are common, presence of a stone is not sufficient for diagnosis of acute calculous cholecystitis.

Many reports of ultrasound sensitivity and specificity cited in reviews are from studies conducted in the 80s and 90s. Since then ultrasound technology has improved. Recent ultrasound machines have resolution great enough to detect stones as small as 2mm in diameter (Brunetti 2015) Therefore, ultrasound's diagnostic accuracy may currently be higher than commonly reported.

Unlike objective findings such as gallbladder wall thickening, the SMS relies on input from the patient and is subjective. Different patients may have varying degrees of tenderness on probing of the gallbladder, and these differences may be further confounded by the use of analgesia prior to the ultrasound. One retrospective cohort study (Nelson et al. 2005) compared the sensitivity and specificity of SMS between patients who had received opioid analgesia and those who had received non-steroidal anti-inflammatory drugs (NSAIDs) or

no analgesia. Including NSAIDs in the control group assumes that NSAID use wouldn't affect the prevalence of SMS, despite the fact that cholecystitis involves an inflammatory process. This study also didn't take into account self-administered analgesia prior to presentation, or other sources of pain relief, for example, the use of gabapentinoids or cannabis. Radiologists involved in this study may have been aware of a patient's analgesia use, therefore ignoring a negative SMS. This study used the emergency department (ED) diagnosis (which is a clinical diagnosis), not pathological diagnosis. Noble et al. (2010) compared the use of 5mg IV meperidine (pethidine) vs. placebo on the presence of SMS in a pilot study. 5mg IV of meperidine is a small dosage (equivalent to 0.5mg IV morphine) (Latta et al. 2002), and unlikely to produce much pain relief or affect SMS. This study used an ED diagnosis if pathological diagnosis was unavailable. This study also didn't take into account self-administration prior to presentation (e.g. a patient may have taken a large dose of controlled release oxycodone before presenting, then been assigned and assessed as a placebo patient, when in fact they have already received opioid analgesia). There is little else in terms of literature on this topic.

We aim to determine the sensitivity and specificity of ultrasound in the diagnosis of acute calculous cholecystitis, in a tertiary care hospital in Australia which uses modern ultrasound technology. We also aim to determine if there is any correlation between administration of analgesia to patients and false negative findings.

We hypothesise that analgesic use will reduce the sensitivity of ultrasound in the diagnosis of acute calculous cholecystitis, due to the fact that analgesics commonly in use have proven efficacy in the treatment of pain.

Objectives

To determine the accuracy of ultrasound for the diagnosis of acute calculous cholecystitis, and the impact of analgesics.

Implementation

This is a retrospective cohort study (chart review) of patients with acute calculous cholecystitis treated with cholecystectomy. The aim of this study is to determine the sensitivity and specificity of ultrasound for the diagnosis of acute calculous cholecystitis, and to evaluate if this is impacted by analgesic use prior to ultrasound. The hypothesis is that analgesia use prior to ultrasound will reduce the sensitivity of ultrasound for the diagnosis of acute calculous cholecystitis. The reasons for a retrospective study rather than prospective, is lack of existing literature on the topic, low expense and simplicity.

Patients will be included based on the following criteria:

- Age 18+
- Patient underwent upper abdominal ultrasound (by radiology department)

- Patient underwent cholecystectomy
- Diagnosis of acute calculous cholecystitis was either confirmed or rejected by pathology (macroscopic and histological analysis)

Gender and ethnicity will not be considered for inclusion.

The reason for this inclusion criteria, is to control for inaccuracies in diagnosis (e.g. an ED diagnosis is not comparable to a pathological diagnosis, and cholecystectomy is required for this). Ultrasound by radiology only is to control for differences in operator technique (emergency physician vs. sonographer).

Patients will be categorised based on analgesia use prior to ultrasound, as follows;

1. No analgesia prior to US
2. Non-opioid analgesia prior to US
3. No or non-opioid analgesia prior to US (category 1+2 combined)
4. Opioid analgesia prior to US

The reason for group 3, is the assumption that any non-opioid analgesic may not be efficacious enough in treating severe biliary pain to mask the SMS. Another reason, is that an opioid analgesic is likely to be given to a patient presenting to ED with severe abdominal pain, therefore, each of groups 1 and 2 individually may not have enough patients to be statistically significant on their own.

For each group, a positive finding will be considered to be a diagnosis of acute calculous cholecystitis by pathology. A negative finding will be pathology showing a result other than that of acute calculous cholecystitis (regardless of ED diagnosis). This is because a pathological diagnosis is the gold standard for diagnosis of acute calculous cholecystitis.

Upon approval, medical records of all patients meeting the inclusion criteria, dating back one year will be retrieved. If the amount of patients meeting the criteria isn't sufficient for the needed sample size (220 as determined using G*Power 3.1 software), then more patients may be included dating back up to a further year to meet this number. The sampling technique used here will be the criterion method (all patients fitting the criteria within the specified time-frame will be included). This is for simplicity and due to an absence of large numbers of patients to randomly sample from.

These medical records will then be categorised into the listed groups by the investigators. Categorisation will occur by viewing the medication list and presenting history to determine if (and what type of) analgesia was either self-administered, or administered by a treating clinician. A patient will be categorised as having received analgesia, only if administration was within a time-frame prior to ultrasound that is shorter than the medication's duration of action. A medication's duration of action will be determined using the MIMS database. If information regarding the typical duration of action isn't available for a specific medication, one typical half-life will be used instead. Data required for the study will be extracted from the original patient medical records and entered into Microsoft Excel (or similar software).

Each patient's ultrasound images and sonography report will be reviewed by a single radiologist. This radiologist will be blinded to the patient's final pathology diagnosis and analgesic use. The radiologist will give a diagnosis of either acute calculous cholecystitis, or a negative finding, based on their own best clinical judgement. The reason for using a single radiologist to review each patient, is to control for inter-radiologist variability in diagnosis, and to blind the radiologist from the patient's analgesia use, which may prompt a diagnosis despite a negative SMS. The patient's radiological diagnosis will then be paired with the corresponding medical record information. Once patient information has been paired with a radiological diagnosis, it will be de-identified. Each patient will be assigned a unique identifier in place of their name.

Patient medical record information will be stored in a locked filing cabinet. Computerised data will be stored on a single password protected computer. After results have been finalised, physical patient information will be shredded, and digital information will be securely deleted. Ultrasound imagery and reports will be viewed only by the single radiologist, using hospital radiology software.

Sensitivity and specificity for ultrasound will be determined for each of the groups by comparing the radiological diagnosis to the final pathology diagnosis. A positive radiological finding with a negative pathology is a false positive, and a negative radiological finding with a positive pathology diagnosis is a false negative.

Statistical analysis will be carried out using "R" software. The Pearson Chi-square test will be used to determine independence. Statistical significance will be $P < 0.05$, and 95% confidence intervals will be calculated. This statistical test will be appropriate because the data will be categorical and nominal (Table 1).

Table 1.

An example of how the analysis will be displayed is as follows:

	(1) No analgesia	(2) Non-opioid analgesia	(3) category 1+2	(4) Opioid analgesia
Sensitivity	- % (± 95% CI)	- % (± 95% CI)	- % (± 95% CI)	- % (± 95% CI)
Specificity	- % (± 95% CI)	- % (± 95% CI)	- % (± 95% CI)	- % (± 95% CI)

Other characteristics for each group will be stated, including; mean age (with standard deviation), gender composition, presence of SMS, and percentage of positive gallbladder pathology.

An ethical issue arising in this study, is the risk of breach of confidentiality of patient information. We will be the only individuals reviewing patient medical record information, and the radiologist will be the only individual reviewing imaging information. Providing information is securely stored, the risk of any further confidentiality breach is minimal. Another ethical issue is the use of patient information with no direct benefit (or compensation) to the actual patients involved. Benefit, however, will be provided to the medical and scientific community.

The potential benefits of this study, is to enhance our knowledge of the accuracy of ultrasound in the diagnosis of this condition, in a major tertiary hospital in 2017-2018. Another benefit is to determine the effect that analgesic use (and its type) has, on the accuracy of diagnostic imaging. This may change the way patients who present with severe abdominal pain are initially managed in an emergency setting, in order to prevent false negative diagnoses. This may be a benefit to future patients, allowing for a higher quality of care. A benefit to society is the prevention of delayed treatment of this condition, or rehospitalisation for emergency surgery. This may result in decreased healthcare costs.

We will apply for ethics review, in order to seek approval to access patient medical record information (Table 2). Patients will not need to be consented, and there will be no patient follow-up or contact. It is not feasible to contact each patient due to the number of patient medical records that will be involved in this study, and there may be difficulties contacting patients who have changed their address or phone number.

Table 2. Patient information.
Data to be collected from a patient's medical record
Patient age
Patient gender
Medications self-administered by patient (according to history), and timing
Medications administered to the patient, and timing
Timing of upper abdominal ultrasound
Final pathology report of gallbladder
Radiological information (to be viewed by single radiologist)
Sonographic images from ultrasound
Sonography report (including probe tenderness)

Author contributions

Study conception and design, drafting of manuscript, critical revision: Jason Friesen.

Critical revision: Dr Brendon Friesen, Dr Ee Syn Tan

Conflicts of interest

The authors have not received any funding, and there is no declared conflict of interest.

References

- Bree R (1995) Further observations on the usefulness of the sonographic Murphy sign in the evaluation of suspected acute cholecystitis. *Journal of Clinical Ultrasound* 23 (3): 169-172. <https://doi.org/10.1002/jcu.1870230304>
- Brunetti JC (2015) Imaging in Gallstones (Cholelithiasis): Overview, Radiography, Computed Tomography. emedicine.medscape.com/article/366246-overview. Accessed on: 2016-6-03.
- Eldar S, Sabo E, Nash E, Abrahamson J, Matter I (1997) Laparoscopic Cholecystectomy for Acute Cholecystitis: Prospective Trial. *World Journal of Surgery* 21 (5): 540-545. <https://doi.org/10.1007/pl00012283>
- Gastroenterological Society of Australia (2016) Gallstones. www.gesa.org.au/resources/patients/gallstones/. Accessed on: 2016-6-03.
- Heuman DM (2016) Gallstones (Cholelithiasis): Practice Essentials, Background, Pathophysiology. emedicine.medscape.com/article/175667-overview#a5. Accessed on: 2016-6-03.
- Latta K, Ginsberg B, Barkin R (2002) Meperidine: A Critical Review. *American Journal of Therapeutics* 9 (1): 53-68. <https://doi.org/10.1097/00045391-200201000-00010>
- Madan AK, Aliabadi-Wahle S, Tesi D, Flint LM, Steinberg SM (2002) How early is early laparoscopic treatment of acute cholecystitis? *The American Journal of Surgery* 183 (3): 232-236. [https://doi.org/10.1016/s0002-9610\(02\)00789-4](https://doi.org/10.1016/s0002-9610(02)00789-4)
- Nelson B, Senecal E, Hong C, Ptak T, Thomas S (2005) Opioid analgesia and assessment of the sonographic Murphy sign. *The Journal of Emergency Medicine* 28 (4): 409-413. <https://doi.org/10.1016/j.jemermed.2004.12.009>
- Nino-Murcia M, Jeffrey RB (2001) Imaging the patient with right upper quadrant pain. *Seminars in Roentgenology* 36 (2): 81-91. <https://doi.org/10.1053/sroe.2001.22825>
- NJ G, G P (2012) 311. Diseases of the Gallbladder and Bile Ducts. *Harrison's Principles of Internal Medicine*. 18. McGraw-Hill, New York, NY.
- Noble V, Liteplo A, Nelson B, Thomas S (2010) The impact of analgesia on the diagnostic accuracy of the sonographic Murphy's sign. *European Journal of Emergency Medicine* 17 (2): 80-83. <https://doi.org/10.1097/mej.0b013e32832e9627>
- Peng WK, Sheikh Z, Nixon SJ, Paterson-Brown S (2005) Role of laparoscopic cholecystectomy in the early management of acute gallbladder disease. *British Journal of Surgery* 92 (5): 586-591. <https://doi.org/10.1002/bjs.4831>
- Pinto F, Pinto A, Russo A, Coppolino F, Bracale R, Fonio P, Macarini L, Giganti M (2013) Accuracy of ultrasonography in the diagnosis of acute appendicitis in adult patients: review of the literature. *Critical Ultrasound Journal* 5: S2. <https://doi.org/10.1186/2036-7902-5-s1-s2>
- Shea JA (1994) Revised estimates of diagnostic test sensitivity and specificity in suspected biliary tract disease. *Archives of Internal Medicine* 154 (22): 2573-2581. <https://doi.org/10.1001/archinte.154.22.2573>
- Trowbridge R, Rutkowski N, Shojania K (2003) Does This Patient Have Acute Cholecystitis? *JAMA* 289 (1): . <https://doi.org/10.1001/jama.289.1.80>