To evaluate the role of Hs-CRP levels in combination with ultrasound findings to predict the difficulty in laparoscopic cholecystectomy-A Prospective study

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BACKGROUND

Very often surgeons come across a number of surgical and technical difficulties due to which the procedure has to be converted into open cholecystectomy. Although 2% to 15% of patients require conversion to open cholecystectomy for various reasons but irrespective of this morbidity and mortality statistics do still favour laparoscopic cholecystectomy over open cholecystectomy.[1] A study was conducted to assess the role of preoperative ultrasonography in predicting failed or difficult laparoscopic cholecystectomy. There were no ultrasound features that identified between the unsuccessful, difficult, or uneventful laparoscopic cholecystectomies. They concluded that detailed preoperative ultrasound evaluation of the gallbladder in patients destined for laparoscopic cholecystectomy is of little value in screening for difficult or unsuitable cases.[2] Adhesions are the important cause for difficulty encountered in LC[3][4] and these cannot be assessed on routine ultrasonography (USG) done for cholelithiasis. Intra abdominal adhesions which lead to increasing difficulty in identifying Calot's triangle and CBD which also predisposes patient to hemorrhage more easily from GB bed and cystic artery and causes increased risk of GB perforation and spillage of gallstones in peritoneal cavity.[5] Severe intra abdominal adhesions make laparoscopic dissection very difficult and is associated with a five fold increase in DLC. Therefore other predictors are required to improve the preoperative assessment of the difficulties encountered during laparoscopic surgery and Hs- CRP has been used as one such investigation. High preoperative CRP, WBC count and ERCP are the predictors of conversion[6]. Surgery for acute cholecystitis in patients with age >65 years and/or CRP level >165 mg/L should be considered as
high risk for conversion[7]. With the help of Hs-CRP the intraoperative findings like intra abdominal adhesions, increasing difficulty in identifying calot's triangle and CBD can be predicted[8]. Association between severity of inflammation as judged by increase in Hs-CRP and failure rate of laparoscopic procedure [9][10][11]. Preoperative Hs-CRP value of 20.64mg/L, can be relied upon as predictors of difficult LC and/or need for conversion not only in the study group in the given population but also in individual cases[12]. Taking in consideration all the above studies the present study is being undertaken to evaluate the role of Hs CRP levels in combination with ultrasound findings to predict difficulty in laparoscopic cholecystectomy so as to improve the patient management.

AIMS AND OBJECTIVES
1. To study the role of Hs-CRP concentration in combination with ultrasound findings to predict the difficulty in laparoscopic cholecystectomy.
2. To study the decrease in concentration of Hs-CRP in laparoscopic cholecystectomy post operatively.

MATERIAL AND METHODS
The study was conducted in the Department of Surgery, Acharya Shri Chander College of Medical Science Jammu. The study being of surgical complexity and for the sake of ethical issues, a total of 100 patients of cholelithiasis and acute cholecystitis consecutively formed the basis of this study. Patients were chosen according to the inclusion and exclusion criteria. Exclusion criteria included, acalculous cholecystitis, choledocholithiasis, autoimmune diseases like rheumatoid arthritis, IBD, lupus, vasculitis, neurodegenerative disease, heart diseases, malignancy, pregnancy, steroid therapy, coagulopathies, local tissue irradiation, acute biliary pancreatic disorder, Mirizzi syndrome, pancreatitis, any state of immunosuppression, previous upper abdominal surgeries. The preoperative workup of the patients included preoperative Hs-CRP and postoperative Hs-CRP specimen. For accurate comparison a fasting morning sample of 5 ml blood was taken in serum activating tubes for sample transfer to microbiology lab for serum collection.

OPERATIVE TECHNIQUE
General anesthesia was used in all patients. Operating timing was recorded from the time of the veress needle insertion to the last skin closure suture. A 1.5-cm longitudinal incision is made at the inferior aspect of the umbilicus, then deepened through the x
gallbladder, or surgical (hemostat) in few cases where bleeding did not stop after giving pressure for 2 to 3 minutes. Both 5-mm graspers were applied to the gallbladder and used to hold it over the right upper quadrant and retrieved from the epigastiric port. In case of spillage of stones, due to perforation of gallbladder the laparoscope was transferred to the subxiphoid port, and an endoscopic retrieval pouch was inserted through the umbilical trocar. The gallbladder was placed in the bag, which was then cinched closed and retrieved through the umbilical port. Romovac drain was put in selected cases where bile spillage or bleeding from liver bed was expected. Final inspection was done to look for bleeding in the liver bed or any spilled stone in case of perforation of gallbladder, wash with normal saline was given. The operating table was returned to the neutral position. The gallbladder bed and the sub hepatic spaces were irrigated and suctioned again with normal saline to ensure adequate hemostasis and removal of any debris or bile that may have spilled. The sub xiphoid port and the two 5-mm ports were removed under direct vision, followed by the Hasson’s trocar. The fascia closed at the umbilical port by using the 2-0 vicryl suture. All of the skin incisions were closed with 2-0 non absorbable mersilk suture. Cyanoacrylate tissue adhesive was used in case of hepatitis-B positive patient.

**RESULT**

Maximum number of patients in our study, were in 50-64 years age group were males being 45.5% and females being 34.3%. Gallstones were present in 100% of patients. According to the ultrasound findings GB wall thickness >4 mm was seen in 9% of patients of which 4 were converted to open cholecystectomy. The Mean±SD of preoperative Hs-CRP was 2.61±.23 and 39 (39%) patients had greater than 0.744mg/dl of Hs-CRP. Of these 39 patients 5 were converted to open cholecystectomy, with a p value of 0.032. Rest of the factors like number of calculi, contracted GB, pericholecystic fluid, USG Murphy’s sign, stones impacted at neck of GB, edematous GB were statistically insignificant. The mean operative time was 50.9±32.85(20-150 minutes), patients with raised Hs-CRP levels had mean OT time of of 78.5±35.13 as compared to mean operative time of 34.3±17.59 with normal Hs-CRP, with a p-value of <0.001, which was statistically significant. In our study the age of the patients ranged from 18-87 years, with a mean of 50.7±15.83 years majority of the patients being in their 5th-6th decade of life, which is consistent with the study conducted by (Al-Azawi D, et al.2007)[9] and sex distribution of their 5th-6th decade of life, which is consistent with the study conducted by (Al-Azawi D, et al.2007)[9] and sex distribution of patients showed that the females (67%) were more than the males(33%), with a male to female ratio of 1:2, which was in accordance with the study conducted by Gupta A, et al.2005)[41]

In our study out of the 89 patients with normal wall thickness on USG of gallbladder, 2 were converted to open. The cause of conversion in one of the patient was torrential bleeding from the cystic artery and in the second he procedure was converted because of distorted anatomy. In 11 patients with thick GB wall on ultrasound i.e. >4 mm, 4 were converted to open, with a p-value of <0.001 which was statistically significant. According to the study of (Lal P, et al.2002)[68] the mean gallbladder wall thickness in his study was 2.8 mm. The maximum gallbladder wall thickness was 6 mm, and the minimum was 1.8 mm. 10 (13.6%) patients had gallbladder wall thickness more than 4 mm of which 9 cases were found to be difficult on surgery, and 5 were converted to the open procedure which is consistent with our findings. According to (Hutchinson CH, et al.1994)[50] thickened gallbladder wall on preoperative ultrasound was correlated with a six times higher conversion rate to open cholecystectomy.

In our study post-operatively after 7 days Hs-CRP had declined, with the mean of 2.14±4.29 compared to pre-operative mean of 2.61±6.23. In our study area under the curve shows that preoperative Hs-CRP with values of >0.730mg/dl is associated with difficult laparoscopic cholecystectomy. In our study diagnostic accuracy of USG combined with preop Hs-CRP in predicting difficult laparoscopic cholecystectomy has a sensitivity of 84.1% with 95% confidence interval of 35.9-99.7 and specificity of 68.7% with confidence interval of 49.7-75.6. In our study postoperatively Hs-CRP with values of >0.730mg/dl had a p value of <0.001 which was statistically significant. In our study, the age of the patients ranged from 18-87 years, with a mean of 50.7±15.83 years majority of the patients being in their 5th-6th decade of life, which is consistent with the study conducted by (Al-Azawi D, et al.2007)[9] and sex distribution of patients showed that the females(67%) were more than the males(33%), with a male to female ratio of 1:2, which was in accordance with the study conducted by Gupta A, et al.2005)[41]

In our study the correlation of preoperative CRP with intraoperative finding/grading in study patients had a p value of <0.001, which was statistically significant. In our study post-operatively after 7-days Hs-CRP had declined, with the mean of 2.14±4.29 compared to pre-operative mean of 2.61±6.23. In our study area under the curve shows that preoperative Hs-CRP with values of >0.730mg/dl is associated with difficult laparoscopic cholecystectomy. In our study diagnostic accuracy of USG combined with preop Hs-CRP in predicting difficult laparoscopic cholecystectomy has a sensitivity of 84.1% with 95% confidence interval of 35.9-99.7 and specificity of 68.7% with confidence interval of 49.7-75.6. Positive predictive Value of 42.6% with confidence interval of 3.89-25.09, and Negative predictive value of 98.5% with CI of 90.7-99.8 with the diagnostic accuracy of 76.7%

In our study visual analog score (VAS) of pain was correlated with Hs-CRP. The hospital stay was correlated with Hs-CRP, with a p-value of <0.001 which was statistically significant. Parenteral analgesic was correlated with Hs-CRP levels, had a p-value of <0.001 which was statistically significant. Oral analgesic was correlated with Hs-CRP, had a p-value of 0.003 which is statistically significant. More analgesic was required in patients with raised Hs-CRP.

**DISCUSSION**

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Gallstones were present in 100% of patients. All of the patients were taken up for laparoscopic cholecystectomy. Hs-CRP levels were seen preoperatively and on 7th postoperative day, and the levels were co-related with the USG findings and intraoperative findings in all 100 patients. The Mean±SD of preoperative Hs-CRP was 2.27±5.33 and 39 patients had greater than 0.744mg/dl of Hs-CRP, and in these patients intraoperative difficulties were encountered. Out of 60 patients with Hs-CRP of <0.744mg/dl, 1 was converted to open. Whereas 34 patients with >0.744mg/dl, 5 were converted to open, with a p value of 0.032 which is statistically significant. These findings were similar to that of (Schafer M, et al.2001)100 which found the Hs-CRP level at admission to be an important predictor of severity of inflammation and failure of early LC in acute cholecystitis. Similarly association between severity of inflammation as judged by increase in Hs-CRP and failure rate of laparoscopic procedure has been reported by (Elder S, et al. 1997)[30]; (Rattraw DW, et al. 1993)[91]; (Bickle A, et al. 1996)[15]; (Wevers KP, et al.2003)[116]; (Asai K, et al.2014)[7]; (Mok KW, et al.2014)[82]; (Teckchandani N, et al.2010)[111]; (Duca S, et al.2003).[29]

In our series Mean operative time was 50.9±32.85 minutes, the range of operative time ranged from 20 minutes to 150 minutes. In our study in patients with normal Hs-CRP the mean operative time was 34.9±17.59 and patients with raised Hs-CRP the mean operative time was 78.5±35.13 with a p value of <0.001, which was statistically significant. In our study more pain, more analgesia and prolonged hospital stay were seen with increased duration of operation, and majority of patients with increased duration of surgery had raised Hs-CRP levels which is consistent with the findings of (Arora BS, et al.2017)[6];(Jackson TD, et al.2011)[51]

Gallbladder was found adherent to the surrounding structures like duodenum, stomach, transverse colon. Hs-CRP levels were raised in 27 patients with flimsy adhesions and in 28 patients with dense adhesions with a p-value of <0.001 which was statistically significant. These findings are consistent with the study by (Peters JH, et al. 1991)[89]; (Meshiikhes AW, et al.1995)[79]; (Underwood, et al.2002)[114]; (Donkervoort, et al.2010)[27]; (Bat Orhan, et al.2015).[12]

According to the Hs-CRP and intraoperative findings patients were divided into three grades. Those patients who were classified into grade 1 laparoscopic cholecystectomy with raised Hs-CRP levels consisted of 3 patients (7.7%). Patients who were classified in grade 2 difficult laparoscopic cholecystectomy with raised Hs-CRP levels consisted of 30 patients (76.9%) and patients who had grade 3 laparoscopic cholecystectomy/converted to open were 6 patients (15.4%). The correlation of preoperative CRP with intraoperative finding/grading in study patients had a p value of <0.001, which was statistically significant meaning that the Hs-CRP concentration is highly significant as predictor of difficult cholecystectomy. (Arora BS, et al.2017)[6]; (Duca S, et al.2003)[29]; (Teckchandani N, et al.2010)[111]

In our series the conversion rate was 6%, which was in contrast to other reported studies. In a series of the 261 patients of laparoscopic cholecystectomy by (Kevin Pett et al.2013)[59] their conversion rate was 24% with 62 cases taken up for OC, while in (Arora BS, et al.2017)[6] series the conversion rate was 10%. In our study the low conversion rate can be attributed to the long experience of the operating surgeon in dealing with the difficult laparoscopic procedures. According to (Knight J, et al.2004)[61] as long as the procedure is carried out by experienced upper gastrointestinal surgeons working within a specialist-led protocol, the conversion rate for laparoscopic cholecystectomy can be as low as 12 per cent. In our study there were 6 patients were converted to open . Out of these 6 cases 3 had gallbladder adherent to surrounding viscera by dense fibro vascular adhesions, and in the other 2 cases had obscured Calot’s triangle. In 1 patient gallbladder was inflamed and sessile leading to severe cystic artery bleed . These findings are similar to that of (Koscak D, et al.2005)[63] who reported in their series that out of 599 cases conversion to open was required in 22(4%) cases, and in 18 of these patients reasons for conversion were numerous solid adhesions on the inflamed gallbladder with adjacent organs.

In the present study we observed levels of Hs-CRP values preoperatively and post operatively. Post-operatively after 7 days Hs-CRP had declined, with the mean of 2.14±4.29 compared to preoperative mean of 2.61±6.23 implying that inflammation is subsiding in postoperative phase which was in accordance with the study of (Arora BS, et al.2017).[6]

According to our study the area under the curve shows that preoperative Hs-CRP of >0.730mg/dl is associated with difficult laparoscopic cholecystectomy. This value possesses 83.33% sensitivity, 62.77% specificity, with a standard error of 0.087 and 95% confidence interval of 0.633 to 0.814 and significance value of 0.0081, for predicting DLC. Similar study was taken up by (Mok KW, et al.2014)[82] evaluated in retrospective cohort parameter that predict DLC or conversion and also described cut off points of CRP for predicting conversion. They found that patients with CRP of <220 (3.2%) had significantly less chance of conversion than those
with CRP >220 (61.9%) (P < .001). According to (Arora BS, et al.2017) the preoperative Hs-CRP value of 20.64mg/L, can be relied upon as predictors of difficult LC and/or need for conversion not only in the study group in the given population but also in individual cases.

Post operative complications included pain, vomiting, fever, basal pneumonitis and wound infections. On day of surgery, pain was seen in 100% of patients for which analgesic was given, fever in 13% of patients, among these 6 patients had raised Hs-CRP preoperatively and 7 had normal Hs-CRP with a p-value of 0.571, which was statistically insignificant. Vomiting was seen in 20% of patients, of which 9 had raised Hs-CRP and 9 had normal Hs-CRP with a p value of 0.362. and wound infection in 3% of patients of which 1 had raised Hs-CRP and 2 with normal Hs-CRP with a p value of 1.000, which was statistically insignificant. Basal pneumonitis was seen in 21% of patients of which 10 had raised Hs-CRP and 11 had normal Hs-CRP with a p value of 0.362. and wound infection in 3% of patients of which 1 had raised Hs-CRP and 2 with normal Hs-CRP with a p value of 1.000, which was statistically insignificant. Wound infection rate was not statistically higher in conversion group (P<0.05) contrary to the findings of (Arora BS, et al.2017).

In our study group there were no cases of common bile duct injury, duodenal injury, colonic injury, trocar site bleeding and no mortality.

In the present series visual analog score (VAS) of pain was correlated with Hs-CRP assessed on the day of surgery at rest which showed a mean of 33.7 with standard deviation of 19.64 in 61 patients with normal Hs-CRP and mean of 68.9 with standard deviation of 20.5 in 39 patients with raised Hs-CRP and had a p value of <0.001 which was statistically significant. VAS of pain was more patients with increased Hs-CRP. (Arora BS, et al.2017)

In the present series parenteral analgesic was correlated with Hs-CRP assessed on the day of surgery where 61 patients with normal Hs-CRP with a mean of 1.3 and standard deviation of 0.67 and patients with raised Hs-CRP were 39 in number with a mean of 2.5 and standard deviation of 0.72 and a p value of <0.001 which was statistically significant in accordance with the study of (Arora BS, et al.2017)

The mean number of oral analgesic tablets consumed 1.4 with a standard deviation of 0.71.Increased number of oral analgesic were consumed by patients with greater than 60 minutes of OT time. Similarly on correlation of oral analgesic following surgery 61 patients with normal CRP with a mean of 1.1 and standard deviation of 0.38 and 39 patients with raised Hs CRP had a mean of 1.8 with a standard deviation of 0.87 and a p-value of 0.003 which was statistically significant. Patients that were converted to open required more oral analgesic as compared to those who underwent laparoscopic cholecystectomy consistent with the findings of (Arora BS, et al.2017).

The hospital stay was correlated with Hs-CRP, 61 patients with normal Hs CRP had a mean of 2.3 and a standard deviation of 0.98 and 39 patients with raised Hs CRP had a mean of 4.2 and a standard deviation of 1.65 with a p value of <0.001 which was statistically significant which is in accordance with the study of (Arora B et al.2017).

Follow up after 1 week quality of life was satisfactory with no case of post operative wound infection, nausea/vomiting or any other late complication. There was no readmission in any of the patients. According to our series diagnostic accuracy of USG combined with preop Hs-CRP in predicting difficult laparoscopic cholecystectomy has a sensitivity of 84.1% with 95% confidence interval of 35.9-99.7 and Specificity of 68.7% and confidence interval of 49.7-75.6. Positive predictive Value of 42.6% with confidence interval of 3.89-25.09, and Negative predictive value of 98.5% with CI of 90.7-99.8 with the diagnostic accuracy of 76%. These observation clearly reflect that determination of Hs-CRP levels combined with ultrasound is an essential tool to selectively workout the patients for OC. Such patients may be taken up for OC to reduce the morbidity and mortality. (Juvonen T,et al.1992)[56]; (Arora BS, et al.2017)[6]; (Ryukyung Lee, et al.2017).[95]

CONCLUSION

We recommend that preoperative estimation of Hs-CRP should be routinely used as an adjunct with ultrasound as an OPD investigation to evaluate degree of expected operative difficulty and selecting out the high risk patients preoperatively. This will help to plan the surgery by arranging the appropriate team of experienced surgeons and to reduce the morbidity/mortality associated with it. The health care costs can also be estimated and conveyed to the patient and unnecessary litigations can also be avoided.