https://doi.org/10.22502/jlmc.v5i1.112 **Original Research Article**

Single dose Intraoperative Antibiotics versus Postoperative Antibiotics for Patient Undergoing Laparoscopic Cholecystectomy for Symptomatic Cholelithiasis: a Randomized Clinical Trial

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ABSTRACT:

Introduction: Surgical site infection is a common complication shown in literature following cholecystectomies. Smaller incision and use of trocars in laparoscopic cholecystectomy lessen the contamination resulting in less chances of surgical site infection. However, in fear of postoperative infection, many opt for the prolonged postoperative use of antibiotic and there is growing consensus against it. Antibiotics not only increases the cost and hospital stay duration but it aids in emergence of multidrug resistance. Because of the controversies, we conducted this clinical trial to see whether a single prophylactic dose of antibiotic at the time of induction of anesthesia for laparoscopic cholecystectomy was equally effective in controlling post-operative infection as multi-dose antibiotics during and post-operative period. **Methods**: The study was conducted at the department of general surgery, Lumbini Medical College Teaching Hospital, from November 2015 to October 2016. All cases with symptomatic cholelithiasis subjected for laparoscopic cholecystectomy were enrolled. Patients were randomized into two groups; Group SD received single dose of an intravenous dose of amikacin 500 mg, at induction of anesthesia and Group MD received multiple intravenous dose of amikacin, during and postoperatively for two days. Complications, hospital stay, and treatment cost in two groups were compared and analyzed. **Results**: There were a total of 240 patients in the study, 118 in Group SD and 122 in Group MD. Post-operative infection rate was 4.2% (n= 5, N=118) in Group SD and 3.3% (n=4, N=122) in Group MD; the difference was not significant (p=0.75). Hospital stay was prolonged and cost was higher significantly in Group MD. **Conclusion**: Single dose of prophylactic antibiotic, administered at induction of anesthesia, is equally effective as multiple doses of post surgical antibiotics to prevent post-operative infection in patients undergoing elective laparoscopic cholecystectomy for uncomplicated cholelithiasis.

Keywords: antibiotics • laparoscopic cholecystectomy • length of hospital stay • prophylactic • surgical wound infection

INTRODUCTION:

At present, laparoscopic cholecystectomy is gold standard for treatment of symptomatic gallstone. The role of prophylactic antibiotic in various clean or clean contaminated surgery reduce the risk of postoperative infective complication thereby reducing morbidity and mortality. Antibiotic prophylaxis are clearly not indicated for most patients undergoing straightforward clean surgical operations in which no obvious bacterial contamination or insertion of a foreign body has occurred.[1] However, clinicians do not give up the tradition of using postoperative antibiotics despite recent evidences supporting single dose prophylactic antibiotic use over multiple doses of antibiotics during and after surgery. A study done in

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our center had shown that amikacin was the most sensitive antibiotic against organisms in bile culture of symptomatic gallstone patients.[2] The over-use of antibiotics can result in more adverse effects, rise in emergence of drug resistant organisms, as well as increased treatment cost.[3] It is not clear whether postoperative use of antibiotic in laparoscopic cholecystectomy, for uncomplicated cholelithiasis and complicated cholelithiasis without features of organ failure, is of any advantage to the patient in terms of preventing infection. The present study aims to evaluate whether single dose of prophylactic antibiotic, administered at induction of anesthesia, is equally effective as multiple doses of post-surgical antibiotics to prevent post-operative infection in patients undergoing elective laparoscopic cholecystectomy for uncomplicated cholelithiasis.

METHODS:

A randomized controlled trial was conducted at Lumbini Medical College Teaching Hospital (LMCTH) from first of November 2015 to 31st of October 2016. The study was approved by the institutional review committee of the college (IRC-LMC). All patients suffering from symptomatic documented gallstones on ultrasonography and undergoing laparoscopic cholecystectomy were included in the study. Patients with complicated gall stones (cholangitis, choledocholithiasis, and pancreatitis) and those who required conversion to open cholecystectomy were excluded. Acute cholecystitis with high leukocyte count (>15,000/ mm^3) and fever (>100°F) prior to surgery were excluded. Patients who were found to have suppurative cholecystitis, empyema, or gangrenous gallbladder during surgery were also excluded. However, patients with acute biliary attack of right upper quadrant pain of less than a week with leukocyte count ≤15,000/mm^3, fever ≤100°F, and without features of organ failure, were included in the study. Those who did not consent to be included in the study were excluded.

All the patients were examined and investigated prior to their surgery, and the information needed was recorded. Before surgery, patients were subjected for simple sequential randomization where an opaque container containing 10 small cheats with number one to 10 written inside it were made. Patient was asked to withdraw one cheat blindly by operating room anesthetic assistant. The cheat was returned back to the same container for next patient. Same process was repeated for each patient. Odd-numbered (1,3,5,7,9) patients received single dose antibiotic prophylaxis (Group SD) of injection amikacin 500mg (AMIKATIL) at induction of anesthesia, whereas even numbered (2,4,6,8,10) received antibiotic prophylaxis of injection amikacin 500 mg (AMIKATIL) at induction of anesthesia and continued at same dose twice a day postoperatively for two days (Group MD). Operation-room anesthetic assistant administered prophylactic antibiotics at induction of anesthesia to all the patients. Group MD patients received additional doses in the ward from ward nurses.

All LCs were performed under general anesthesia with endotracheal intubation by the surgeons experienced in the procedure. The abdominal skin was prepared with 10% povidone-iodine solution. Laparoscopic instruments were sterilized as per hospital protocol before procedures (overnight dipping in Suma Med Enzyme, a special enzymatic liquid detergent formulated to elimination of dirt in the cleaning of medical instruments in soft-medium water; and dipping in 2% gluteraldehyde one hour before surgery). Aseptic precaution was maintained throughout the procedure. After dissection of gall bladder from GB fossa, epigastric port was used for extraction of gall bladder; those found difficult due to thick wall or large stone size for extraction were retrieved through umbilical port. Patients were monitored postoperatively in recovery room for two hours and then send to post anesthesia care unit as per our existing practice.

For postoperative analgesia, injection ketorolac 30 mg intravenously, every eight hours, was administered on the day of operation, and was switched to oral combination of paracetamol 500 mg and ibuprofen 400 mg from next day. Oral feeding was started after six hours of surgery. Drip was stopped once oral feeding was tolerated with cannula being locked in situ. Patients in Group SD were discharged on second postoperative day after first dressing if vitals were stable, no features of peritonitis was present, and patients tolerated oral feeds. Patients on Group MD were discharged on third postoperative day after receiving antibiotics for 48 hours. Patients from both groups were advised to follow up in surgical out-patient clinic on eight post operative day for suture removal and 30th postoperative day with reports of histopathology of resected gallbladder. Status of wound (normal, inflamed, or pus) was recorded and managed accordingly with anti-inflammatory drugs thrice daily for inflammation and dressing of wound in case of pus. Pus was subjected for culture and sensitivity testing.

Patient's demographics and clinical characteristics including gall bladder perforation and bile/stones spillage during surgery, use of suction, status of wound were recorded in a pre-designed proforma. Data were entered into Microsoft Excel 2013 and were analyzed with SPSS-23. Descriptive statistics was presented as mean, standard deviation, frequency, and percentage. Student-t test was used to compare continuous data, Chi-square test was used to compare categorical data. *P* value of 0.05 was considered significant.

RESULTS:

A total of 240 patients were included in the study. There were 118 (49.2%) patients in Group SD and 122 (50.8%) in Group MD. Mean age of patients in Group SD and Group MD was 44.19 year (*SD*=16.18) and 51.31 year (*SD*=14.50) respectively. This difference in mean was statistically significant (t=3.59, df=238, p<0.001) with patient in Group SD being younger than those in Group MD. There were 71.2% (n=84, N=118) female in group SD and 54.9% (n=67, N=122) female in Group MD and this difference was statistically significant (X^2[N=240, df=1] = 6.8, p=0.009). Twenty-four patients in total presented with features of acute biliary attack. Seven of them were in Group SD and 17 in Group MD and this difference was statistically not significant (X^2[N=24, df=1] = 2.2, p=0.24). Intra-operative biliary spillage was seen in 18.6% (n=22, N=118) in Group SD and 21.3% (n=26, N=122) in Group MD. This difference was comparable (X^2[N=240, df=1] = 0.27, p=0.6). Port contamination was more common (8.5%, n=10, N=118) in Group SD as compared to Group MD (4.1%, n=5, N=122), however the difference was not significant (X^2[N=240, df=1] = 1.96, p=0.19). Duration of surgery was comparable in two groups (t=0.79, df=238, p=0.43). Mean duration in Group SD was 42.84 min (*SD*=28.66) and in Group MD was 40.12 min (*SD*=24.67). Mean length of hospital stay in Group MD (M=3.15 days, *SD*=0.36) was significantly longer (t=32.47, df=238, p<0.001) than that in Group SD (M=2.02 days, *SD*=0.13). Average treatment cost in Group MD was NRs 28973.89 (*SD*=557.55) and for patients in Group SD was NRs 23320.55 (*SD*=503.77); treatment cost was significantly higher in Group MD (t=82.33, df=238, p<0.001).

Table 1 shows the rate of surgical site infections in two groups, the difference was not statistically significant. All infections occurred at epigastric port except one in the Group SD which occurred in umbilical port. The later was managed with stitch removal, laying open of the wound, collection of swab for culture and sensitivity, anti-inflammatory drug, but no empirical antibiotic. Culture did not reveal any growth of micro-organisms. Daily dressing was followed by secondary suturing on the third post-operative day.

Table 1: Wound infection between two groups

	Wound infection, n (%)	No wound infection, n (%)	p
Group SD (n=118)	5 (4.24%)	113 (95.76%)	0.75 (Fisher exact)
Group MD (n=122)	4 (3.28%)	118 (96.72%)	

Wound erythema was seen in equal number in both group (n=4 each) and managed with oral anti-inflammatory drugs. Most of the case with wound erythema (n=3) and stitch abscess (n=1) might had port contamination during delivery of GB from the epigastric port. Patient with stitch abscess has associated controlled hypothyroidism. No patient of either group developed deep infection, seroma formation, or other complications. None of the patient developed any complication in a follow up period of one month.

Among diabetic patients, 44.4% (n=4, N=9) developed postoperative wound infection whereas only 2.1% developed infection among non-diabetic patients. This difference was significant (p<0.001, Fisher exact test).

Table 2 shows the relationship between diabetes status and treatment group among those patients who developed postoperative surgical site infection. There was no significant association between the presence of wound infection in diabetes in patients receiving single dose of antibiotic compared to those receiving multiple dose antibiotic.

Table 2: Infection in two group and diabetes status

	Group SD	Group MD	*P*
DM with infection	1	3	0.2 Fisher exact
Non DM with infection	4	1	

DISCUSSION:

Surgical site infection is presumed to be a common problem associated with clean-contaminated and contaminated surgical procedures. SSI increases hospital stay, hospital cost and patient morbidity and mortality. The use of prophylactic antibiotic is believed to make the surgical outcome better and has been a trend ever since the era prior to the introduction of minimal invasive Laparoscopic cholecystectomy two decades ago. Laparoscopic cholecystectomy is an elective clean operation with very low post-operative wound infection rate.[4,5] In Laparoscopic cholecystectomy, the incision is smaller and manipulation is done through trocars that lessen the contamination and exposure of wound, unlike in open surgery.[6,7] Secondly, the better preservation of immune system following less tissue trauma and non-violation of mucosal defense barrier of the respiratory, gastro-intestinal or genital epithelium lessen the incidence of infections following laparoscopic cholecystectomy; the need for postoperative antibiotics is now frequently questioned.[8] The main aim of our study is to evaluate the impact of single dose versus multiple dose antibiotics in preventing postoperative SSI in elective laparoscopic cholecystectomy. All cholecystectomy patients at our hospital routinely receive antibiotic prophylaxis (amikacin 500 mg IV) prior to surgery.[2]

The mean age in our study was 44 years in patient receiving single dose antibiotics and 51 years in patient receiving multiple dose of antibiotics. There should have been no significant difference in the mean age between randomized groups. We don't have a clue on how that happened. Maybe this was due to simple randomization. This is one of the weakness of this study.

In the present study, the SSI was slightly higher in Group SD but it was not significantly different. Our findings are comparable with reported studies.[6,9-11] In a randomized controlled trial by Gaur et al. on 417 patients undergoing laparoscopic cholecystectomy, an overall infection rate was 2.2%, which is consistent with the results obtained in our study.[12]

In the present study, we had higher incidence of bile spillage (20%, *n*=48, *N*=240). Possible cause could be involvement of acute cases (10%) and different levels of operating surgeons, though all of them were experienced about the procedure. Findings of this study does not support the general perception that bile leak increases the SSI. Out of 22 bile spillage in Group SD (118 LC), there were only five SSIs, out of which only three had intraoperative bile spillage. Similarly, in Group MD (122 LC), there were 26 bile spills, but none of the four SSIs had any history of bile spill. Other studies have reported similar findings.[13,14] We did not include body mass index (BMI) as a possible variable to influence wound infection in open surgery, because BMI is not considered a risk factor in minimal invasive LC with small incision. In case of LC, studies have not found differences in operative time, length of stay, or complications between normal-weight and overweight or obese patients.[15]

There was significant difference in average hospital stay after surgery, with 2.02 days in Group SD and 3.15 days in Group MD. Our practice is to discharge patients on the second postoperative day following LC unless their condition was complicated (example: unstable vitals or peritonitis due to bile leak) or they were not willing to go home (due to transportation problem when living far from the hospital). In this study, we had no bile leak or duct injury. Our hospital policy is to admit patients for elective surgery one day prior to surgery for pre-anesthetic checkup. In Group MD patients, we give antibiotics post-operatively for 48 hours, so they have to stay longer than patients in Group SD. Because of the longer hospital stay and the cost of antibiotic for 48 hours, the average treatment cost for patients in Group MD was significantly higher.

There are some limitations in the study; as we did not include patients with acute cholecystitis with high leukocyte count (TLC>15000/mm^3), fever on admission (Temp.>100°F), or findings of suppurative cholecystitis, empyema, or gangrenous gallbladder during surgery. Thus, these findings cannot be generalized to all patients who undergo surgery for acute cholecystitis because they are already on antibiotic when admitted from emergency department. This will require separate study. Admitted patients at our institute are subjected for cholecystectomy within a week of attack, on any of the six scheduled operation days. Otherwise, they are advised for surgery after six weeks or more. We consider “emergency cholecystectomy surgery” out of normal operating schedule only if suspicious for complication such as peritonitis due to gangrenous or gallbladder perforation.

As the risk of SSI in LC is low, so even for uncomplicated cases of acute cholecystitis (TLC ≤ 15000 with temp. ≤ 100°F), single dose of prophylactic antibiotics will suffice, as we found in this study. Based on recent published evidences and after the completion of our own study, we have now adopted the policy of not administering postoperative antibiotics in uncomplicated cases of LC. This study is hoped to help other institutions in Nepal as well as in other developing countries with similar socioeconomic condition to benefit from its findings.

CONCLUSIONS:

For laparoscopic cholecystectomy, a single dose of prophylactic antibiotic, administered at the time of induction of anesthesia, is equally effective in reducing the surgical site infection as compared to multiple intra and post-operative doses of antibiotics in patients undergoing elective laparoscopic cholecystectomy for uncomplicated cholelithiasis and those with marginally raised leukocytes and low-grade fever. Post-operative continuation of antibiotics only increases the treatment cost and hospital stay without any effect on SSI.

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