Original Article

Prophylactic antibiotics at the time of elective cholecystectomy are effective in reducing the post-operative infective complications: a systematic review and meta-analysis

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Background: The objective of this article is to evaluate the role of prophylactic antibiotics in preventing the infective complications in patients undergoing elective laparoscopic cholecystectomy (ELC).

Methods: A systematic review of the literature on the published randomized, controlled reporting the role of prophylactic antibiotics in preventing the infective complications in patients undergoing ELC was undertaken using the principles of meta-analysis.

Results: Twenty-five RCTs on 6,138 patients evaluating the infective complications in patients undergoing ELC were systematically analysed. There were 3,099 patients in antibiotics group and 3,039 patients in no-antibiotics group. The risk of surgical site infection (SSI) [odds ratio (OR), 0.75 (95% CI, 0.52–1.07), P=0.11], distant infection [OR, 0.66 (95% CI, 0.21–2.14), P=0.49] and residual abscess [OR, 0.93 (95% CI, 0.23–3.81), P=0.92] was lower in the antibiotics group but statistical significance was not reached. However, the risk of overall all type of infective complications was statistically lower [OR, 0.69 (95% CI, 0.50–0.95), P=0.02] in the antibiotics group. Subsequently, this was reflected into the reduced length of hospitalization [standardized mean difference (SMD), −0.32 (95% CI, −0.54–−0.10), P=0.004] in the antibiotics group.

Conclusions: Use of prophylactic antibiotics at the time of induction in patients undergoing ELC has clinically proven advantage of reducing the post-operative infective complications.

Keywords: Gallstones; cholecystectomy; surgical site infection (SSI); post-operative infections

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Introduction

The most frequent complication in patients undergoing cholecystectomy is surgical site infection (SSI) (1). The direct costs of SSI is due to prolonged hospitalization, re-admissions, frequent visits in the outpatient department and/or emergency visits, additional surgical procedures, and antibiotics therapy for an extended time period. Furthermore, the list of supplementary direct costs may continue to rise from the compulsory radiological procedures, laboratory investigations, frequent visits of health-care community workers at home, other ancillary services, and specialized levies. Indirect economic burden of SSI is very challenging to measure which may include lost productivity of the patient, a temporary or permanent decline in physical, reduction in the functional or mental capacity of the patient and reduced health-related quality of life (2-6). Since the introduction of laparoscopic cholecystectomy for the management of benign gallbladder disorders, it has undergone several innovative and dramatic changes. Although minimal invasive surgery for gallbladder surgery has offered several advantages due to reduced tissue handling and tissue trauma but prophylactic use of antibiotics to prevent SSI has not altered. In laparoscopic cholecystectomy the incisions are smaller compared to open cholecystectomy, and the wounds are not directly exposed to microbiological contamination of operative filed because all manipulations of the excised organ are made through a trocar that isolates the surgical wound. Therefore, contemporary clinical trials started focusing on the re-evaluation of the practicality of antibiotic prophylaxis in elective laparoscopic cholecystectomy (ELC). The meta-analyses (7-10) of randomized, controlled trials investigating the beneficial and harmful effects of prophylactic antibiotics to prevent SSI in patients undergoing ELC, failed to demonstrate advantages of antibiotics in term of SSI but horizon of overall postoperative complications and distant infective complications was over-sighted either intentionally or un-intentionally. The purpose of this meta-analysis is to re-visit the published evidence and attempt to generate latest evidence whether prophylactic antibiotics reduce the incidence of SSI as well as all types of post-operative infective complications.

Methods

Electronic data base search

Medline (via PubMed), Embase, Scopus, Cochrane Colorectal Cancer Group (CCCG) Controlled Trial Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library and Science Citation Index Expanded were explored until March 2018 to find relevant published RCTs. The search terms were constructed based on patients, interventions/comparators, and outcomes as follows:

- ❖ Patients: all patients with cholecystitis, cholelithiasis, gallstones.
- ❖ Intervention/comparator: intravenous antibiotics at the time of induction.
- ❖ Outcomes: length of stay in hospital, all infective complications, superficial SSI, deep SSI, distant infections and deep space infection.

The MeSH terms related to the gall stones, cholecystectomy and prophylactic intravenous antibiotics were identified from the PubMed and subsequently inserted in the search boxes of other electronic databases. Attempts to find extra trials were also made by the hand searching of the references of published studies.

Data management

Two reviewers (MSS, JB) independently searched and selected studies and disagreements were resolved by consensus. Inclusion criteria were as follows: RCTs on patients with gallstones needing laparoscopic cholecystectomy; induction time administration of intravenous antibiotics as prophylactic dose to prevent SSI; and had at least one outcomes of interest as described above. The studies were included regardless of sample size, origin of study, age of the participant, gender of the participant and the language in which the study was published.

Interventions

The administration of single dose of intravenous antibiotics as prophylactic measure to prevent SSI.

Outcome of interest

We evaluated the length of stay in hospital, all infective complications, superficial SSI, deep SSI, distant infections and deep space infection. These outcomes were defined according to the original studies.

Risk of bias assessment

The methodological quality of the included studies was assessed by MSS and SR as recommended by the Cochrane Collaboration using the "Risk of Bias Assessment Tool". This included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. Disagreement was resolved by a third reviewer (KKS). The critical appraisal tool to score the quality of included trials was also adopted from the published guidelines of Jadad *et al.* (11) and Chalmers *et al.* (12). The short summary of the resulting evidence was presented in a tabulated form by using tool GradePro® (13), provided by the Cochrane Collaboration.

Statistical analysis

The efficacy of single dose of intravenous antibiotics was

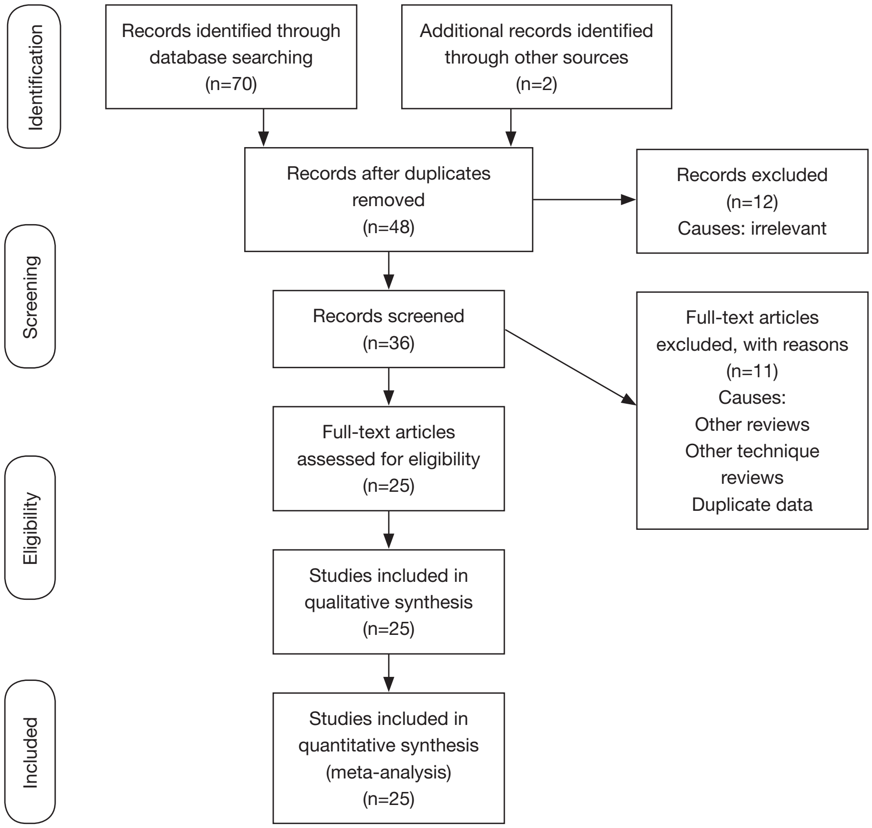

Figure 1 PRISMA flow diagram.

directly compared and pooled for each outcome of interest if there were at least two studies for each comparison. The odds ratio (OR) and standardized mean difference (SMD) were estimated and pooled across studies using a random-effect model. Heterogeneity was assessed using Cochrane Q test and I^2 statistic. The statistical analysis of the data was conducted according to the guidelines provided by the Cochrane Collaboration including the use of RevMan 5.3® statistical software, and the use of forest plots for the graphical display of the combined outcomes (14-19).

Results

The PRISMA flowchart regarding literature search outcome and study screening pattern is explained in *Figure 1*. Twenty-five randomized, controlled trials (20-44) on 6,138 patients compared the use of prophylactic induction-time antibiotics. There were 3,099 patients recruited in antibiotics group and 3,039 patients were in no-antibiotics group. The quality of included randomized, controlled trials was moderate to high on Jadad & Chalmers scoring system owing to the utilization of computer generated randomization technique, optimum implementation of power calculations encompassing issues of type I and type II errors, adequate concealment protocol, blinding and the use of intention-to-treat analysis. The short summary and generated evidence is presented in *Figure 2* analysed on GradePro.

Overall postoperative infective complications

There was no heterogeneity [Tau^2 =0.00, chi^2 =18.97, df =23, (P=0.70); I^2=0%] among included trials. In the random effects model analysis (OR, 0.69; 95% CI, 0.50–0.95; Z=2.27; P=0.02), the risk of developing postoperative infective complications was statistically lower in patients receiving prophylactic antibiotics prior to undergoing ELC (*Figure 3*).

Superficial and deep wound SSI

There was no heterogeneity [Tau^2 =0.00, chi^2 =12.32, df =23, (P=0.97); I^2=0%] among included trials. In the random effects model analysis (OR, 0.75; 95% CI, 0.52–1.07;

Summary of findings:

Prophylactic antibiotics versus no-antibiotics in elective laparoscopic cholecystectomy compared to cholecystectomy for

Patient or population:
Setting:
Intervention: Prophylactic antibiotics versus no-antibiotics in elective laparoscopic cholecystectomy
Comparison: cholecystectomy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with cholecystectomy	**Risk with Prophylactic antibiotics versus no-antibiotics in elective laparoscopic cholecystectomy**				
All types of infective complications assessed with: Odds ratio follow up: range 1-4 weeks to	**Study population**		**OR 0.69** (0.50 to 0.95)	6138 (25 RCTs)	⊕⊕⊕⊕ HIGH	
	37 per 1,000	**26 per 1,000** (19 to 35)				
	Moderate					
	33 per 1,000	**23 per 1,000** (17 to 31)				
SSI assessed with: Odds ratio follow up: range 1-4 weeks to	**Study population**		**OR 0.75** (0.52 to 1.07)	6037 (25 RCTs)	⊕⊕⊕⊕ HIGH	
	28 per 1,000	**21 per 1,000** (15 to 30)				
	Moderate					
	26 per 1,000	**20 per 1,000** (14 to 28)				
Hospital stay assessed with: Standardised mean difference follow up: mean 1-4 weeks	-	-	-	2556 (7 RCTs)	⊕⊕⊕⊕ HIGH	SMD -0.32 (-0.54 to -0.1)
Deep infection assessed with: Odds ratio follow up: range 1-4 weeks to	**Study population**		**OR 0.93** (0.23 to 3.81)	2246 (8 RCTs)	⊕⊕⊕⊕ HIGH	
	4 per 1,000	**3 per 1,000** (1 to 14)				
	Moderate					
	0 per 1,000	**0 per 1,000** (0 to 0)				
Distant infections assessed with: Odds ratio follow up: range 1-4 weeks to	**Study population**		**OR 0.66** (0.21 to 2.14)	3167 (12 RCTs)	⊕⊕⊕⊕ HIGH	
	20 per 1,000	**13 per 1,000** (4 to 42)				
	Moderate					
	9 per 1,000	**6 per 1,000** (2 to 19)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Figure 2 GradePro summary of evidence.

Study or Subgroup	Antibiotics Events	Antibiotics Total	No-antibiotics Events	No-antibiotics Total	Weight	Odds Ratio M-H, Random, 95% CI
Chang 2006	1	141	2	136	1.7%	0.48 [0.04, 5.34]
Chen 2000	2	57	3	56	3.0%	0.64 [0.10, 4.00]
Csendes 1995	2	50	2	55	2.5%	1.10 [0.15, 8.15]
Dobay 1999	0	29	0	24		Not estimable
Fang 2006	2	263	2	372	2.6%	1.42 [0.20, 10.13]
Harling 2000	3	39	3	37	3.6%	0.94 [0.18, 5.00]
He 2003	3	70	2	68	3.1%	1.48 [0.24, 9.13]
Higgins 1999	7	277	3	135	5.4%	1.14 [0.29, 4.48]
Hu 2004	1	98	1	98	1.3%	1.00 [0.06, 16.22]
Illig 1997	1	128	4	122	2.1%	0.23 [0.03, 2.11]
Koc 2003	1	49	1	43	1.3%	0.88 [0.05, 14.43]
Kuthe 2006	1	40	2	53	1.7%	0.65 [0.06, 7.47]
Mahatharadol 2001	0	50	1	50	1.0%	0.33 [0.01, 8.21]
Matsui 2014	6	518	35	519	13.3%	0.16 [0.07, 0.39]
Naqvi 2013	8	177	7	173	9.4%	1.12 [0.40, 3.17]
Ruangsin 2014	2	150	5	149	3.7%	0.39 [0.07, 2.04]
Shah 2012	6	154	9	156	9.1%	0.66 [0.23, 1.91]
Sharma 2010	2	50	4	50	3.3%	0.48 [0.08, 2.74]
Shi 2001	3	64	3	55	3.8%	0.85 [0.16, 4.41]
Tocchi 2000	5	44	7	40	6.6%	0.60 [0.18, 2.08]
Turk 2013	4	278	2	269	3.5%	1.95 [0.35, 10.73]
Uludag 2009	7	68	7	76	8.3%	1.13 [0.38, 3.41]
Wang 2002	2	100	2	100	2.6%	1.00 [0.14, 7.24]
Wang 2007	2	100	2	100	2.6%	1.00 [0.14, 7.24]
Yildiz 2009	4	105	3	103	4.4%	1.32 [0.29, 6.05]
Total (95% CI)		**3099**		**3039**	**100.0%**	**0.69 [0.50, 0.95]**
Total events	75		112			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 18.97$, df = 23 (P = 0.70); $I^2 = 0\%$
Test for overall effect: Z = 2.27 (P = 0.02)

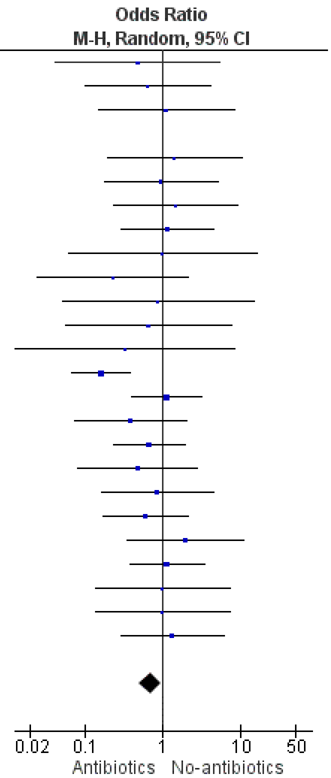

Figure 3 Forest plot for all types of postoperative infective complications in patients undergoing elective laparoscopic cholecystectomy. Odds ratio is shown by 95% confidence interval.

Z=1.61; P=0.11), the risk of developing superficial and deep wound SSI was lower in antibiotics group but it could not reach the statistical significance (*Figure 4*).

Deep space SSI

There was no heterogeneity [Tau^2 =0.00, chi^2 =3.35, df =4, (P=0.50); I^2=0%] among included trials. In the random effects model analysis (OR, 0.93; 95% CI, 0.23–3.81; Z=0.11; P=0.92), the risk of developing superficial and deep wound SSI were similar in both groups (*Figure 5*).

Distant infections

There was moderate heterogeneity [Tau^2 =1.39, chi^2 =14.27, df =6, (P=0.03); I^2=58%] among included trials. In the random effects model analysis (OR, 0.66; 95% CI, 0.21–2.14; Z=0.68; P=0.49), the risk of developing distant infections was lower in antibiotics group but it could not reach the statistical significance (*Figure 6*).

Duration of hospital stay

There was significant heterogeneity [Tau^2 =0.06, chi^2 =31.99, df =5, (P<0.00001); I^2=84%] among included trials. In the random effects model (OR, −0.32; 95% CI, −0.54–−0.10; Z=2.85; P=0.004), the duration of hospital stay was statistically shorter in patients who received prophylactic antibiotics (*Figure 7*).

Discussion

Summary of main results

Based upon the findings of current study of 25 RCTs on 6,138 patients evaluating the infective complications in patients undergoing ELC, the risk of SSI, distant infection and residual abscess was lower in the antibiotics group but statistical significance was not reached. However, the risk of overall all type of infective complications was statistically lower in the antibiotics group reflecting the reduced length of hospitalization in the antibiotics group. This

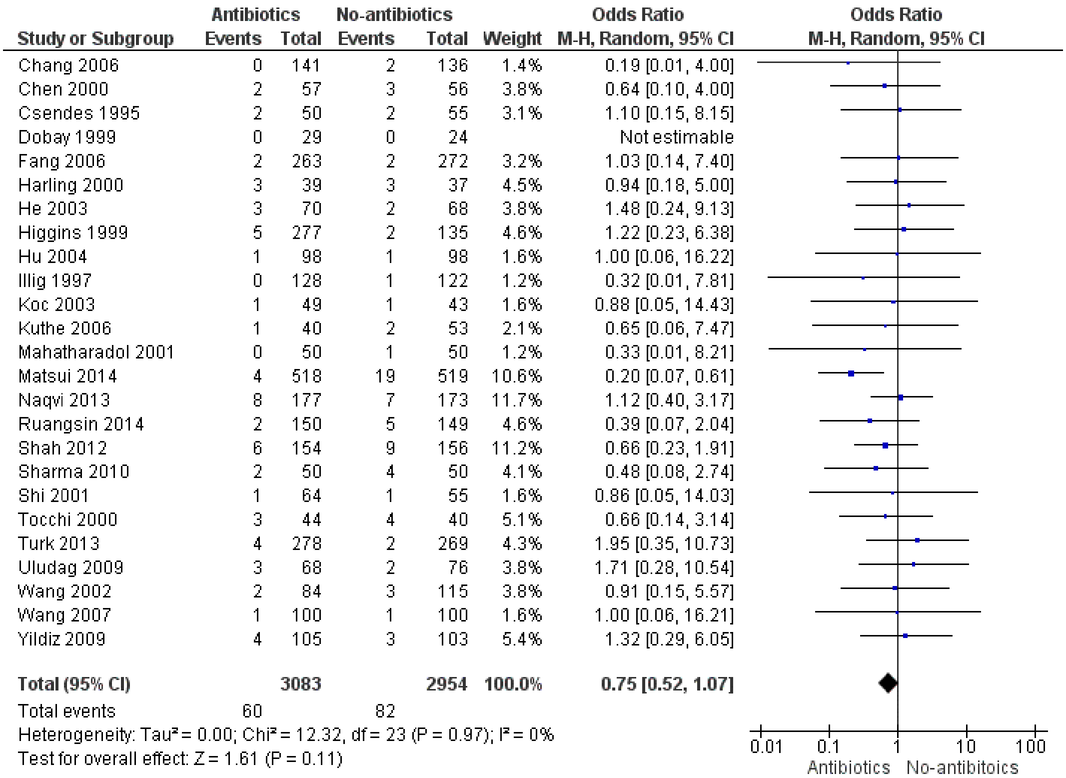

Figure 4 Forest plot for superficial and deep wound surgical site infection (SSI) in patients undergoing elective laparoscopic cholecystectomy. Odds ratio is shown by 95% confidence interval.

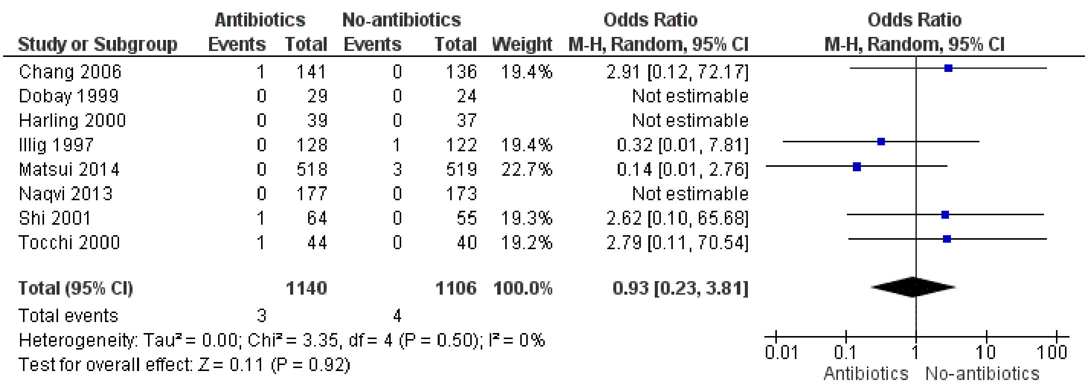

Figure 5 Forest plot for deep space surgical site infection (SSI) in patients undergoing elective laparoscopic cholecystectomy. Odds ratio is shown by 95% confidence interval.

study is the first ever review reporting the advantages of using prophylactic antibiotics in patients undergoing ELC to prevent infective complications of all types instead of looking at SSI only.

Overall completeness and applicability of evidence

The resulting evidence presented in this article is pertinent to patients undergoing ELC only does not investigate the

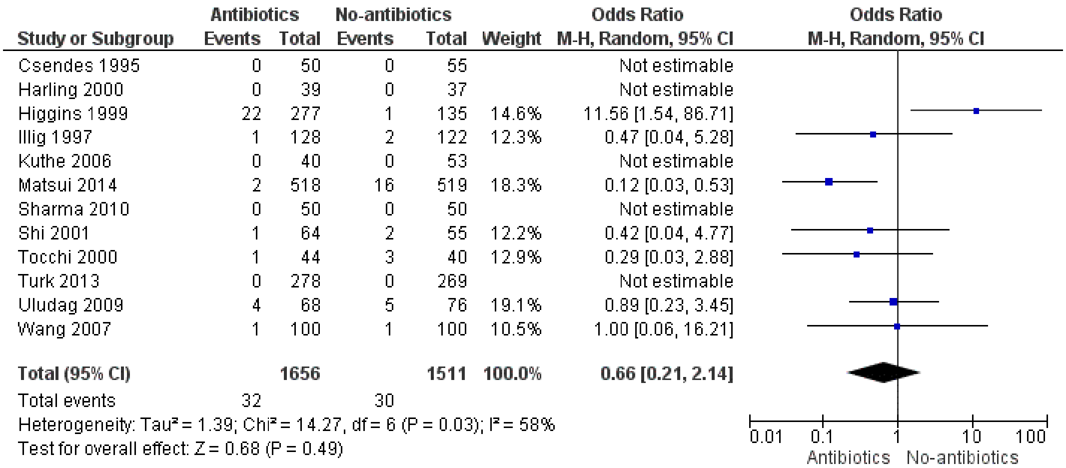

Figure 6 Forest plot for distant infections in patients undergoing elective laparoscopic cholecystectomy. Odds ratio is shown by 95% confidence interval.

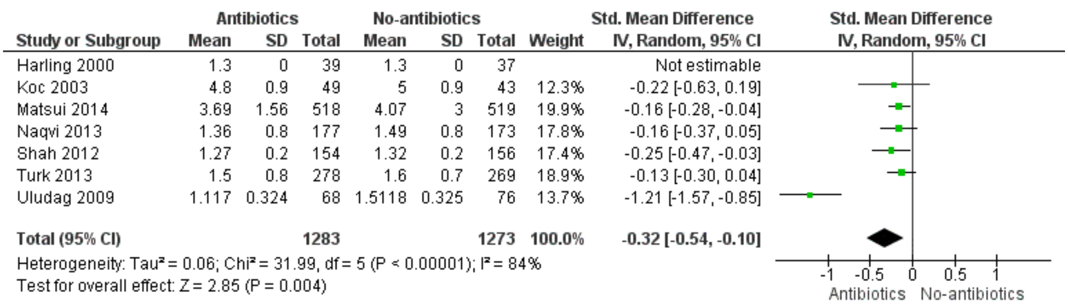

Figure 7 Forest plot for length of hospitalization in patients undergoing elective laparoscopic cholecystectomy. Odds ratio is shown by 95% confidence interval.

extended role of prophylactic antibiotics in patients with hot gallbladder. Despite the reporting of several systematic reviews and meta-analyses (7-10) reporting and arguing the non-beneficial role of prophylactic antibiotics for a decade or so, only current study provide evidence on the beneficial role of prophylactic antibiotics and it may be acceptable to recommend the routine use of antibiotics at induction time in patients undergoing ELC.

Quality of evidence

This study reports a total of 6,138 participants from 25 randomized, controlled trials undergoing ELC reporting post-operative infective complications of all types as primary outcome preferentially to highlight the beneficial or non-beneficial role prophylactic antibiotics. The risk of bias in the included trials was very low when scored against the standard quality guidelines and therefore, the quality of resulting evidence may be considered adequate (*Figure 2*). The bile spillage rate and the need of antibiotics on "as required" bases were inadequately reported in the included trials and therefore, an isolated sub-group analysis of these patients was not possible. This phenomenon may have influenced the final outcome of infective complications. Other confounding factors which might have influenced the final outcome of the postoperative infective complications include the use of variable number and size of ports for ELC; type, duration and dosage of antibiotics; use of extraction endo-bag at surgeons' discretion; and use of placebo versus no-placebo in non-antibiotics group.

Potential biases in the review process

Authors implemented the standard Cochrane Collaboration methodology to perform the statistical analysis, interpretation as well as to present the quality of evidence. The low risk of bias was mainly attributable to the presence of blinding and allocation concealment in the majority of the studies. Presence of adequate randomization technique and optimum utilization of the power calculations in all included trials provided adequate strength to generate higher level of evidence. The bile spillage rate and the need of antibiotics on "as required" bases were inadequately reported in the included trials and therefore, an isolated sub-group analysis of these patients was not possible. This phenomenon may have influenced the final outcome of infective complications. Other confounding factors which might have influenced the final outcome of the postoperative infective complications include the use of variable number and size of ports for ELC; type, duration and dosage of antibiotics; use of extraction endo-bag at surgeons' discretion; and use of placebo versus no-placebo in non-antibiotics group.

Agreement and disagreement with other published evidence

The findings of current meta-analysis are not in accordance with the conclusions of the previously published reviews (7-10) which demonstrated that the use of prophylactic antibiotics in patients undergoing ELC did not reduce SSI rate. However, this study provides up to date, comprehensive and cumulative evidence favouring the use of prophylactic antibiotics on these patients to reduce overall post-operative infective complications rather focusing on SSIs only.

Implications for practice and future research

This study quite successfully validate that the prophylactic use of antibiotics is effective in reducing the post-operative infective complications in patients undergoing ELC. However, the aforementioned confounding factors potentially influencing the final outcomes must be acknowledged and attempts must be made to generate less biased evidence by removing these limitations. These results cannot be generalized in all patients undergoing ELC because the prophylactic strategy for post-operative infective complications is multi-dimensional which also include pre-operative and per-operative measures for optimum reduction. Evaluation of infective complications in group of patients with perforated gallbladder during ELC needs another randomized, trial comparing with non-perforated gallbladder to find the necessity and duration of antibiotics prophylaxis. In addition, trials targeting type and duration of antibiotics prophylaxis are also required to avoid study sample contamination by modifiable confounding factors.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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