

ANSWERING REVIEWERS



Monday, March 17th 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS Manuscript NO: 7910-review.doc).

Title: Effects of Laparoscopic Cholecystectomy on Lung Function. A Systematic Review.
(Number ID: 01200740. Special issue celebrating the 20th anniversary of anniversary of WJG (15): Laparoscopic resection of gastrointestinal tract.)

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 7910 - review

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to reviewers' suggestions.

Particularly, the suggestions made by the first reviewer (02456611) were as following: **1.** to include tables either in the main document or supplementary file of the: a. Quality of the study, b. Description of the baseline characteristics of the individual studies; **2.** In order to improve the concise of the article, references and the statistical process charts should not appear in the body of text; **3.** Sensitivity analysis should be performed to explore the potential heterogeneity, because there is significant heterogeneity in figure 1 and 2.

1. a. The quality of the study has been determined by defining the quality of the literature reviewed for the writing of our work. We have specified the number of citations of the articles we have used, being published after 1/1/1990, and the total Impact Factor (IF) of their corresponding journals. The number of citations was found to be 1,502 in 927 overall hits on February 28th 2014 while the total IF was calculated to 69.176 (Page 9 of the submitted revised manuscript)

b. The description of the baseline characteristics of all the individual studies we have used for the writing of our manuscript has been added in Table 1, Table 2 and Table 3 (Pages 7,8,9 of the submitted revised manuscript).

2. Also, references do not appear in the body of text because they have been included in the aforementioned Tables 1, 2 and 3 (Pages 7,8,9 of the submitted revised manuscript) marked by their exponent number as they appear in the References/Section of the manuscript.

The statistical process charts (Figure 1 and Figure 2) do not appear in the body of text of the revised manuscript, and they have been submitted as separate files.

3. Sensitivity analysis for the exploration of the potential heterogeneity has also been performed (Pages 16, 17, 18 of the submitted revised manuscript).

The second reviewer (00057983) suggested that since the papers studied have been listed in the references, the authors should mark the reference numbers in the main context to make it more concise. The above suggestion has been done by having incorporated these papers in Tables 1, 2 and 3 (Pages 7,8,9 of the submitted revised manuscript) marked by their exponent number as they appear in the

References/Section of our article.

Besides, quality of the study, Tables 1, 2 and 3 and Sensitivity analysis are enclosed in the Format for ANSWERING REVIEWERS as follows:

Quality of the Study:

Moreover, to determine the quality of the literature reviewed in our study, we determined the number of citations of these articles since 1/1/1990 and the total Impact Factor (IF) of their corresponding journals. The number of citations was found to be 1,502 in 927 overall hits on February 28th 2014 while the total IF was calculated to 69.176. Both citations and impact-factors were provided by the Hellenic National Documentation Center (page 9 in the Main Manuscript).

Tables : Table 1 (page 7 in the Main Manuscript), Table 2 (page 8 in the Main Manuscript), Table 3 (page 9 in the Main Manuscript), Table 5 (page 17 in the Main Manuscript), Table 6 (page 18 in the Main Manuscript).

TABLE 1: Description of the baseline characteristics for the articles selected from the first literature search (as described in the evidence acquisition section).	
1.	Fraze et al.^[17] :Comparative measurements of FVC, FEV ₁ and FEF _{25%-75%} variables preoperatively and on the 1 st postoperative day after LC and OC.
2.	Hall et al.^[18] :Comparison of the incidence of postoperative pulmonary complications (collapse/consolidation, unexplained temperature >38°C and positive sputum microbiology) after LC and OC.
3.	Coskun et al.^[19] :Comparative measurements of the FVC, FEV ₁ , Tiffeneau index, PEF and MEF _{25%} variables before and 24 hours after LC and OC.
4.	Damiani et al.^[20] :Comparative meta-analytic study focusing on the evaluation of the Tiffeneau index after LC and OC.
5.	Osman et al.^[21] :Comparative measurements for FVC, FEV ₁ , Tiffeneau index and ABGs variables preoperatively and on the first day after LC and OC.
6.	Putensen-Himmer et al.^[22] : Comparative measurements for FVC, FEV ₁ , FRC and ABGs variables preoperatively and up to the 3 rd postoperative day after LC and OC.
7.	Mealy et al.^[23] : Comparative measurements for FVC, FEV ₁ , PF, ABGs, urinary cortisol, vanillylmandelic acid, metanephrines and nitrogen loss, CRP, ESR and pain analogue scale preoperatively and up to 48 hours after LC and OC.
8.	Williams et al.^[24] : Comparative measurements for FVC, FEV ₁ and Maximum Forced Expiratory Flow Rate preoperatively and after LC and OC, according to patient's cooperation.
9.	Gunnarson et al.^[25] : Comparative measurements for FVC, FEV ₁ and ABGs variables before surgery and two hours and the first day after LC and OC.
10.	Karayiannakis et al.^[26] : Comparative measurements for FVC, FEV ₁ , FRC, FEF _{25%-75%} and ABGs variables preoperatively and on the second day after LC and OC.
11.	Hendolin et al.^[27] : Comparative measurements for FVC, FEV ₁ , Peak Flow Velocity and arterial oxygen tension variables and measurements for plasma concentrations of catecholamines, cortisol and glucose preoperatively, in the recovery room and on the first day after LC and OC.
12.	Hasukic et al.^[28] : Comparative measurements for FVC, FEV ₁ , FEF _{25%-75%} , Peak Expiratory Flow and ABGs variables preoperatively and on the first day after LC and OC.
13.	Bablekos et al.^[29] : Comparative measurements of lung volumes (FVC, VC, ERV, IC, FRC, RV/TLC variables), flow rates (FEV ₁ , Tiffeneau index, PEF, FEF _{25%-75%} variables) and ABGs parameters

	<i>preoperatively, on the 2nd and on the 8th day after LC and OC.</i>
14.	Ravimohan et al.^[30] : Comparative measurements for FVC, FEV ₁ , FEF _{25%-75%} , PEF, Tiffeneau index and ABGs parameters preoperatively, on the first and on the sixth postoperative day after LC and OC.
15.	Bablekos et al.^[31] : Comparative measurements of Control of Breathing indices (V _T , BF, T _I , T _I / T _{TOT} , Po.1, Zminsp) and airway resistance (Raw) preoperatively, two days and eight days after LC and OC.
16.	McMahon et al.^[32] : Minute ventilation, arterial carbon dioxide tension, end-tidal CO ₂ tension, peak airway pressure and arterial oxygen levels were studied just before operation and at the time of gallbladder removal during LC and OC.
17.	Mimica et al.^[36] : Examination of the influence of physical therapy on both the values of respiratory parameters, such as FVC, FEV ₁ , Tiffeneau index, and ABGs variables preoperatively and to the sixth day after LC and OC.
18.	Farrow et al.^[72] : The authors showed that LC is associated with significantly less morbidity compared with OC. Variables such as FVC and FEV ₁ along with the occurrence of postoperative pulmonary complications and narcotic doses were studied preoperatively to the third day after LC and OC.
19.	Redmond et al.^[75] : Parameters determining the immune function such as monocyte superoxide anion (O ₂ ⁻) and tumor necrosis factor release, neutrophil O ₂ ⁻ levels and chemotaxis, serum cortisol and CRP were studied prior to surgery and on the first and third days after LC and OC.
20.	Kimberley et al.^[84] : FVC, FEV ₁ , Maximum voluntary handgrip strength (HGS) and maximal inspiratory pressure (MIP) were studied preoperatively and on the first day after LC and OC.

TABLE 2: Description of the baseline characteristics for the articles selected from the second literature search (as described in the evidence acquisition section).	
1.	Johnson et al.^[109]: Preoperative and postoperative measurements 24 hours after LC of VC, FRC, arterial PO ₂ and chest-X-ray atelectasis.
2.	Poulin et al.^[110]: Postoperative values of FVC and FEV ₁ variables measured on the first day after LC compared with values of the respective pulmonary function indices recorded on the first day after upper abdominal surgery and cholecystectomy.
3.	Schulze et al.^[108]: Assessments of pain scores, peak flow values and subjective feeling of fatigue preoperatively, six hours postoperatively and daily during the first week after operation for patients having undergone LC.
4.	Schauer et al.^[77]: Comparative measurements for FVC, FEV ₁ , FEF _{25%-75%} , Tiffenueau Index, FEF _{MAX} , total lung capacity and oxygen saturation preoperatively to ten days after surgery between LC and OC.
5.	Saunders et al.^[92]: Measurements of FVC and the potential emergence of respiratory and gastrointestinal disturbances preoperatively to the first postoperative day between LC and OC.
6.	Torrington et al.^[93]: Comparative evaluations for FVC and FEV ₁ and arterial blood gases between LC and OC preoperatively and 24hours after surgery.
7.	Chumillas et al.^[34]: Comparative examination for FVC, FEV ₁ and arterial oxygenation values between LC and OC, from preoperatively up to 48hours after surgery.
8.	Hasukic S and Mesic D^[111]: Comparative measurements for FVC, FEV ₁ , FEF _{25%-75%} and arterial oxygenation preoperatively and 24hours after surgery between LC and OC (included in the statistical analysis).

Table 3: Description of the baseline characteristics for the six additional articles used in the writing of this review.	
1.	Chuter TAM et al.^[91]: Parameters of respiratory pattern such as minute ventilation, tidal volume, the contribution of chest wall (V_C / V_T) to tidal volume and the contribution of the abdominal wall (V_{ab} / V_T) to tidal volume were studied preoperatively, on the first and on the third day after OC.
2.	Rademaker BM et al.^[81]: FVC, FEV ₁ and peak expiratory flow(PEF) were examined in a half sitting position preoperatively, and 24hours postoperatively in patients having undergone elective LC and OC while the effects of thoracic epidural analgesia after LC were also studied.
3.	McMahon AJ et al.^[99] : FVC, FEV ₁ , PEF, postoperative pain scores, analgesic consumption and oxygen saturation were examined preoperatively, on the first postoperative day and on the second postoperative day between patients who underwent LC and OC. The OC was performed with minilaparotomy surgical approach
4.	Freeman JA and ArmstrongIR^[82] : Measurements of FVC, FEV ₁ , Tiffenueau index, FRC, TLC, inspiratory and expiratory mouth pressures were examined preoperatively, and 24hours postoperatively between LC and OC.
5.	Rovina N et al.^[83]: Measurements of FVC, FEV ₁ , Tiffenueau index, blood gases indices, maximum static inspiratory (PI_{max}) and maximum expiratory (PE_{max}) muscle pressures were studied preoperatively, on the first postoperative day and on the second postoperative day between LC and OC.
6.	Mimica Z et al.^[33]: Spirometric parameters (FVC, FVE ₁ , Tiffenueau index), arterial blood gases, abdominal circumference, intestinal peristalsis and defecation were studied preoperatively, to the sixth postoperative day between LC and OC.

Sensitivity analysis

Significant heterogeneity between groups reflects the different effect of each treatment. The heterogeneity within each treatment group should be investigated, but there is in all studies lack of consistent information focusing on explanative factors. The most reported variable in papers is age, which is comparable. By visual inspection of the forest plots we can identify the studies responsible for heterogeneity.

In *FVC* variable (**Table 5**), by removing Mealy et al.^[23] and Kimberley et al.^[84] from the *LC* group; and Karayannakis et al.^[26] and Rademaker et al.^[81] from the *OC* group there is no significant heterogeneity ($I^2= 0.0\%$ and 6.8% ; $p\text{-value}=0.645$ and 0.379 , respectively for *LC* and *OC*). The pooled standardized mean difference (*SMD*) changed slightly from -1.074 to -0.933 in the *LC* and from -2.152 to -1.773 in the *OC* group. The overall *SMD* changed from -1.455 to -1.245 .

In *FEV₁* variable (**Table 6**), there was no significant heterogeneity in the *LC* group. By removing Mealy et al.^[23] from the *OC* group there is no significant heterogeneity ($I^2= 36.4\%$; $p\text{-value}=0.127$). The *SMD* in the *OC* group was slightly changed from -2.186 to -2.059 and the overall *SMD* from -1.497 to -1.422 .

We could not identify the reason that these few studies differ from the rest and produce heterogeneity in the results.

In any case, the random effects pooled estimate is appropriate when significant heterogeneity is evident.

Table 5. FVC sensitivity results.

Study	SMD	95% Conf. Interval	% Weight	
LC				
Putensen-Himmer et al.	-0.937	-1.866 to -0.009	3.0	
Gunnarssonn et al.	-0.803	-1.392 to -0.214	7.4	
Karayannakis et al.*	-0.697	-1.138 to -0.257	13.1	
Hendolin et al.	-0.920	-1.504 to -0.336	7.5	
Hasucik et al.	-0.649	-1.169 to -0.13	9.5	
Mimica et al.	-1.197	-1.624 to -0.771	14.1	
Freeman and Armstron	-0.752	-1.364 to -0.139	6.8	
Bablekos et al.*	-0.905	-1.593 to -0.218	5.4	
Mimica et al.	-1.197	-1.624 to -0.771	14.1	
Hasukic et al.	-0.649	-1.169 to -0.13	9.5	
Rademaker et al.	-1.198	-2.158 to -0.238	2.8	
Rovina et al.*	-1.320	-1.922 to -0.718	7.1	
Sub-total				
I-V pooled SMD	-0.933	-1.093 to -0.773	100.0	
D+L pooled SMD	-0.933	-1.093 to -0.773		
OC				
Putensen-Himmer et al.	-1.637	-2.664 to -0.61	5.0	
Gunnarssonn et al.	-2.785	-3.932 to -1.637	4.0	
Hendolin et al.	-1.970	-2.695 to -1.244	9.9	
Hasucik et al.	-1.656	-2.266 to -1.046	14.0	
Mimica et al.	-1.973	-2.452 to -1.493	22.7	
Bablekos et al.*	-1.000	-1.935 to -0.065	6.0	
Mimica et al.	-1.596	-2.048 to -1.145	25.6	
Kimberley et al.	-3.373	-6.206 to -0.54	0.7	
Rovina et al.*	-1.748	-2.403 to -1.092	12.2	
Sub-total				
I-V pooled SMD	-1.771	-1.999 to -1.542	100.0	
D+L pooled SMD	-1.773	-2.014 to -1.531		
Overall				
I-V pooled SMD	-1.208	-1.339 to -1.077		
D+L pooled SMD	-1.245	-1.468 to -1.022		
Test(s) of heterogeneity				
	Heterogeneity	Degrees of		
	statistic	freedom	p-value	I-squared
LC	8.75	11	0.645	0.0%
OC	8.59	8	0.379	6.8%
Overall	52.01	20	<0.001	61.5%

*48 hrs

Table 6. FEV₁ sensitivity results.

Study	SMD	95% Conf. Interval	% Weight
LC			
Putensen-Himmer et al.	-0.796	-1.710 to 0.118	3.1
Mealy et al.	-1.090	-2.036 to -0.143	2.9
Karayannakis et al.*	-0.706	-1.147 to -0.265	13.4
Hendolin et al.	-0.920	-1.504 to -0.336	7.6
Hasucik et al.	-1.000	-1.538 to -0.462	9.0
Mimica et al.	-1.463	-1.906 to -1.021	13.3
Freeman and Armstron	-0.913	-1.535 to -0.290	6.7
Bablekos et al.*	-1.045	-1.744 to -0.346	5.3
Mimica et al.	-1.463	-1.906 to -1.021	13.3
Hasukic et al.	-1.000	-1.538 to -0.462	9.0
Kimberley et al.	-1.167	-1.725 to -0.608	8.3
Rovina et al.*	-0.794	-1.36 to -0.229	8.1
Sub-total			
I-V pooled SMD	-1.068	-1.229 to -0.907	100.0
D+L pooled SMD	-1.068	-1.229 to -0.907	
OC			
Putensen-Himmer et al.	-1.540	-2.55 to -0.529	5.0
Karayannakis et al.*	-1.756	-2.273 to -1.238	19.2
Hendolin et al.	-1.980	-2.707 to -1.253	9.7
Hasucik et al.	-2.078	-2.732 to -1.424	12.0
Mimica et al.	-2.500	-3.026 to -1.974	18.6
Bablekos et al.*	-1.286	-2.257 to -0.314	5.4
Mimica et al.	-2.500	-3.026 to -1.974	18.6
Kimberley et al.	-5.099	-8.978 to -1.220	0.3
Rovina et al.*	-1.964	-2.644 to -1.285	11.1
Sub-total			
I-V pooled SMD	-2.091	-2.318 to -1.865	100.0
D+L pooled SMD	-2.059	-2.359 to -1.760	
Overall			
I-V pooled SMD	-1.412	-1.543 to -1.28	
D+L pooled SMD	-1.422	-1.688 to -1.156	
Test(s) of heterogeneity			
	Heterogeneity	Degrees of	
	statistic	freedom	p-value
			I-squared
LC	10.70	11	0.468
OC	12.58	8	0.127
Overall	75.31	20	<0.001

*48 hrs

3. References and typesetting were corrected according to Journal's **Format for references**.
Our references number is 111. The PMID number has been inserted but DOI number was not found for all references.

4. As for the Language evaluation, both reviewers gave us Grade B (minor language polishing). As all authors we are no-native speakers of English, we made use of a copyediting service provided by a professional English language editing company (American Journal Experts: <http://www.aje.com>). The e-mail sent to us confirming the copyediting of our manuscript (along with the ESPS Ms NO: 7910) is enclosed in the Format for ANSWERING REVIEWERS.

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Dear Dr. George D. Bablekos,

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I encourage you to explore your account, where you can receive coupons for referring your colleagues or providing a testimonial and learn about our other services.

It was a pleasure to edit this manuscript; good luck with the publication process.

Sincerely,

Benjamin G.

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Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

George D. Bablekos^{1,2} MD, PhD, Thoracic Surgeon

A handwritten signature in black ink, appearing to read 'G. Bablekos', with a long horizontal flourish extending to the right.

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