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Interleukin-6 levels after open and laparoscopic Nissen's fundoplication for gastro-oesophageal reflux disease: A short meta-analysis

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ABSTRACT

Objectives: A meta-analysis of published literature comparing interleukin-6 (IL-6) levels after open Nissen's fundoplication (ONF) versus laparoscopic Nissen's fundoplication (LNF) for gastro-oesophageal reflux disease. **Methods:** Electronic databases were searched from January 1991 to October 2009. A systematic review was performed to obtain a summative outcome. **Results:** Two randomized controlled studies were analyzed. There were 30 patients in the laparoscopic group and 30 in the open group. There was no significant heterogeneity among trials ($Q = 0.08$, $df = 1$, $p < 0.77$, $I^2 = 0$). There was no significant difference between LNF and ONF [fixed effects model: $SMD = -0.05$, 95% CI (-0.54, 0.43), $z = -0.21$, $p = 0.83$; random effects model: $SMD = -0.05$, 95% CI (-0.54, 0.43), $z = -0.21$, $p = 0.83$]. **Conclusions:** There appears to be no difference in IL-6 levels after ONF or LNF in the immediate period after surgery, however there few studies and further randomized trials are needed to strengthen the evidence. © 2010 Trade Science Inc. - INDIA

KEYWORDS

Laparoscopy;
Fundoplication;
Gastroesophageal reflux;
Nissen's;
Interlukin-6.

INTRODUCTION

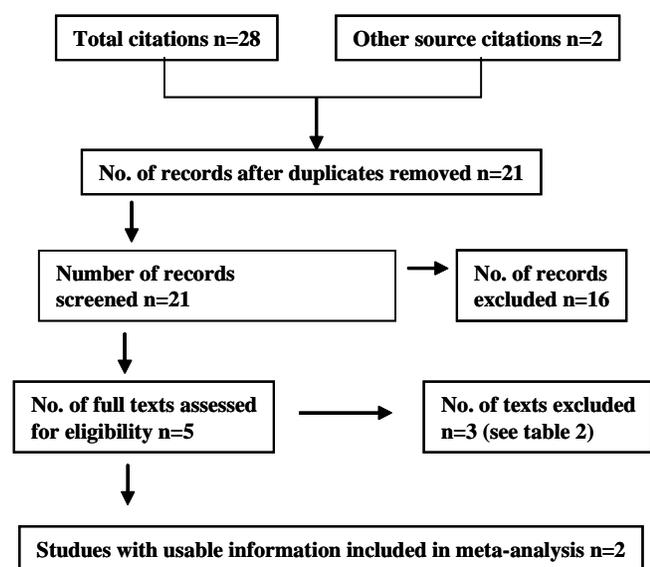
Laparoscopic surgery has been shown to have clinical advantages over open procedures in relation to reduced hospital stay, less blood loss and quicker recovery^[1]. It is postulated that these benefits may be due to reduced surgical trauma^[2] and subsequent proportional change of inflammatory and immunological processes^[3]. These changes have been reported after laparoscopic cholecystectomy^[4] however few studies have been randomized and some authors argue that the degree of

dissection does not isolate the response just to laparoscopic technique itself. Fundoplication has less extensive dissection and may therefore be a more appropriate procedure to compare immunological and inflammatory outcomes^[5]. Interlukin-6 (IL-6) is a mediator of acute-phase trauma response and often correlate well with extent of surgical trauma^[6].

The objective of this article is to meta-analyse the published literature examining interleukin-6 levels after open Nissen's fundoplication (ONF) and laparoscopic Nissen's fundoplication (LNF).

METHODS

All randomized controlled trials examining IL6 levels after LNF versus ONF for GORD, between January 1991 and October 2009 were identified. We searched the MEDLINE, EMBASE, CINAHL and PubMed databases available online. The text words “minimally invasive”, “keyhole surgery”, “heartburn”, “reflux disease” and “immune function” were used in combination with the medical subject headings “laparoscopy”, “fundoplication” and “gastroesophageal reflux”. A flow chart of the literature search according to PRISMA guidelines^[7] is shown in figure 1.



Statistical analyses were performed using Comprehensive Meta-Analysis 2006® for Windows XP. Hedges g statistic was used for the calculation of standardized mean differences (SMD). The SMDs were combined using inverse variance weights in the fixed effects model and the DerSimonian and Laird method

in the random effects model^[8]. In each case a heterogeneity test was carried out to see whether the fixed effects model was appropriate. In a sensitivity analysis, 0.5 was added to each cell frequency for trials in which no event occurred in either technique of reversal, according to the method recommended by Deeks et al.^[9]. Forest plots were used for the graphical display.

RESULTS

Five studies^[3,5,10-12] discussing IL-6 after LNF and ONF were retrieved from the electronic databases. Two studies^[11,12] were included in our study according to our inclusion criteria (TABLE 1). Three trials^[3,5,10] were excluded (TABLE 2). Characteristics of each trial are given in TABLE 3. There were 30 patients in the laparoscopic group and 30 in the open group. The outcome variables are shown in TABLE 4. The methodological quality of included trials is assessed in TABLE 5^[13,14]. The Mantel-Haenszel fixed effect model was used to compute robustness and susceptibility to any outliers among these trials.

IL-6 levels within 2 hours of surgery

Two studies^[11,12] contributed to a summative outcome. There was no significant heterogeneity among trials ($Q = 0.08$, $df = 1$, $p < 0.77$, $I^2 = 0$). There was no significant difference between LNF and ONF [fixed effects model: $SMD = -0.05$, 95% CI (-0.54, 0.43), $z = -0.21$, $p = 0.83$; random effects model: $SMD = -0.05$, 95% CI (-0.54, 0.43), $z = -0.21$, $p = 0.83$; figure 2].

DISCUSSION

Suppression of the immune system is a well known

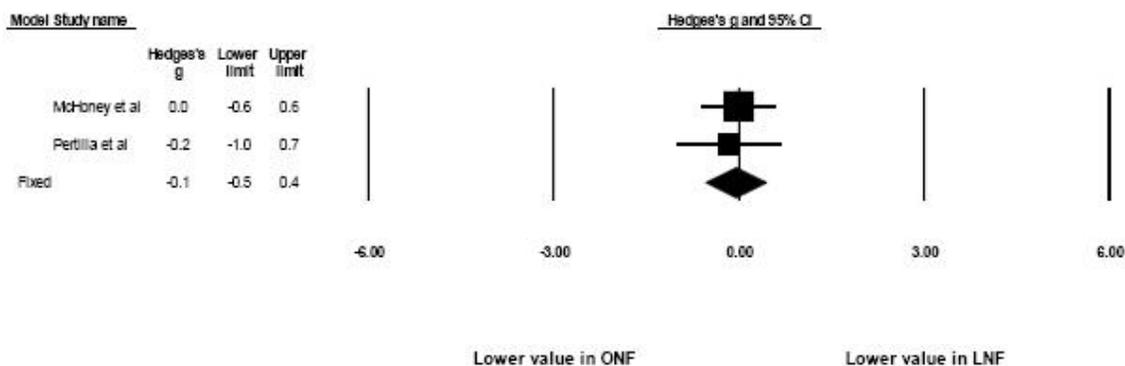


Figure 2 : Biochemical and immunological markers-IL6<2hrs after surgery

Minireview

TABLE 1 : Inclusion criteria

- All studies comparing laparoscopic with conventional Nissen fundoplication for gastro-oesophageal reflux.
- All randomized controlled trials.
- Trials on patients of any age and sex.
- Trials in all languages.

TABLE 2 : Excluded trials

Trial	Reason for exclusion
Zieren et al. 2000	Non-randomized study
Sietses et al. 1999	Immune function without IL6 testing
Hansen et al. 1998	Not exclusive to Nissen fundoplication

TABLE 3 : Treatment protocols for trials

Trial	Year	Type	N	Type	Trial protocol
McHoney et al.	2005	Open lap	20 20	Randomised Controlled Trial	Paediatric population. Blood samples taken pre-operatively and immediately post-operatively.
Pertilla et al.	1999	Open lap	10 10	Randomised Controlled Trial	Adult population. Blood samples taken pre-operatively and immediately post-operatively.

TABLE 4 : Immediate post-operative immunological outcomes

Trial	Year	Type	Immune response	
			IL6	
			<2h after surgery	
McHoney et al.	2005	Open lap	20.3 (0.4-38.4)	
			20.3 (4.2-34.1)	
Pertilla et al.	1999	Open lap	12.5 (sd = 14.1)	
			15.1 (sd = 18.2)	

TABLE 5 : Modified quality score for randomized controlled trials (Jaddad et al. & Chalmers et al.)

Quality variables	McHoney et al.	Pertilla et al.
Was the study described as randomized such as using the words randomly, random, and randomization? [0,1]	1	1
Was randomization described and appropriate? [-1,0,1]	1	1
Was the study described as double blind? [0,1]	0	0
Was method of blinding appropriate? [-1,0,1]	0	0
Was there a description of withdrawals and dropouts? [0,1]	1	1
Inclusion Criteria	1	1
Exclusion Criteria	1	0
Study Period Given	0	0
Appropriate statistical analysis	1	1
Hard End Points	1	1
Sample size calculation	0	0
Baseline comparable	1	1
Any missing post op data	1	1
Allocation concealment	0	0
Analysis by intention to treat	0	0
Score	9	8

Score Max 15, Poor = -1-5, Fair = 6-10, Good = 11-15

sequelae of surgery^[15]. IL-6 is one acute phase response mediator and acts as a marker for surgical trauma. It may have a role in inducing C-reactive protein (CRP) synthesis^[6] and could therefore have potential clinical implications in identifying inflammatory processes before CRP.

Our meta-analysis shows no difference in IL-6 levels between LNF and ONF in the immediate period after surgery. This may be due to the increased length of time taken by LNF^[12]. It may also be due to a dampening effect produced by stimulation of the vagus nerve^[16,17], hence immediate differences may not be apparent. Both trials were consistent with having no significant difference between the 2 techniques^[11,12]. This is further corroborated by Zieren et al who reported no difference in the early period after surgery^[5].

There was not enough data to meta-analyse IL-6 levels beyond 2 hours post-operatively however the literature suggests that IL-6 is higher in ONF after 2 hours compared with LNF. Pertilla et al.^[12] describes a 2 fold increase in IL-6 levels after ONF on the 2nd post operative day compared with LNF and approached statistical significance ($p = 0.075$). Zieren et al.^[5], in a prospective study, corroborates this result and goes fur-

ther by noting a significantly higher IL-6 level in ONF compared with LNF after 4 hours, 1 day, 4 days after the operation. However in a 2nd randomized study significant differences were not achieved at 4 hours and 1 day post-operatively although actual rises were higher in the ONF group.

This finding is in keeping with a lack of significant changes between ONF and LNF in some other immunological markers such as interleukin-10 and tumour necrosis factor alpha levels^[11].

Sietses et al.^[3] reports other markers of immune function such as HLA-DR expression which remained suppressed up to 4 days after the operation. Other studies report higher interleukin-1 receptor antagonist in ONF^[11].

The paucity of data in the literature and variable cytokine response to surgery^[10] means conclusions are difficult to draw, however there is evidence to suggest a tendency towards less immunosuppression in LNF compared with ONF beyond 2 hours post-operatively.

CONCLUSION

There appears to be no difference in IL-6 levels after ONF or LNF in the immediate period after surgery, however there few studies and further randomized trials are needed to strengthen the evidence.

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