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Laparoscopic versus open surgery for complicated appendicitis: a randomized controlled trial to prove safety

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Laparoscopic versus open surgery for complicated appendicitis: a randomized controlled trial to prove safety

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Abstract

Background

To date, no randomized control trial has been performed comparing open appendicectomy (OA) to laparoscopic appendicectomy (LA) in complicated appendicitis. A systematic review and meta-analysis in 2010 concluded LA is advantageous to OA with less surgical site sepsis in complicated appendicitis; however, the level of evidence is weak (level 3a).

The aim of the study was to determine whether LA is safe in the treatment of complicated appendicitis.

Methods

One hundred and fourteen patients were randomized prospectively to either OA or LA using a computer generated blind method. Patients who were either less than 12 years of age, had previous abdominal surgery or were pregnant were excluded. A team of senior surgeons capable of doing both OA and LA performed all procedures.

Primary outcome included all-cause mortality and procedure-related mortality; secondary outcomes included intra-operative duration, rates of wound sepsis and re-intervention, length of hospital stay and re-admission rates. The trial was registered with Current Control Trials (ISRCTN92257749).

Results

The intra-operative duration, the rate of wound sepsis, the number of re-operations, the length of hospital stay and the rate of re-admissions between the OA and LA groups did not differ statistically.

Conclusion

Laparoscopic appendicectomy is safe in complicated appendicitis.

Acknowledgements

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A special thank you to Hermina Tau who made this dissertation possible thanks to her diligent work. Her dedication to this dissertation is greatly appreciated.

Deirdré Kruger has been immensely helpful with her statistical analysis and the proof reading of this dissertation.

Lastly the entire dissertation would not have been possible without the expertise of the following surgeons Christine Jann-Kruger, Akos Kiss and JAO Omoshoro-Jones.

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Abbreviations

Open appendicectomy (OA)

Laparoscopic appendicectomy (LA)

Standard deviation (SD)

C-reactive Protein (CRP**)**

Randomized control trials (RCT)

Candidate's declaration

I, John-Edwin Thomson, declare that this dissertation is my own work. It is being submitted for the degree of Master in Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

The results of this trial have been published in Surgical Endoscopy Journal

Thomson J-E, Kruger D, Jann-Kruger C et al (2015). Laparoscopic versus open surgery for complicated appendicitis: a randomized controlled trial to prove safety. Surg Endosc. Jul;29(7):2027–32. (Appendix 3)

_____

Dr John-Edwin Thomson

29 June 2015.

Dedication

This dissertation is dedicated to my wonderful wife, Nicky Thomson.

Chapter 1

Introduction

Appendicectomy is the most commonly performed emergency surgical procedure, with an individual life time incidence of 6–8 % (1). Since its introduction by McBurney (2) over a century ago, open appendicectomy (OA) has been the gold standard for the treatment of appendicitis. However, with the advent of laparoscopy and the introduction of a laparoscopic appendicectomy (LA) by Semm in 1983 (3), LA has become an alternative surgical approach for the treatment of appendicitis.

Randomized control trials (RCTs) in uncomplicated appendicitis have demonstrated that LA is a safe alternative to OA (4–10) with less wound sepsis (8, 9, 11–21, 27), shorter hospital stay (8, 12, 14, 15, 19, 20, 22–25) and quicker return to work (8, 11, 15, 17, 19, 20, 25, 26). Sauerland et al. (20) concluded that LA seemed to have various advantages over OA; however, intra-abdominal abscess formation was three times more common in the LA group. Piskun et al. (27) concluded that there was no difference in the rate of postoperative intra-abdominal abscesses between OA and LA in complicated appendicitis.

A number of trials have shown that LA is safe and feasible in complicated appendicitis (28–32); however, no RCT has been performed to directly compare LA to OA in complicated appendicitis. Subgroup analyses from RCTs designed for uncomplicated appendicitis suggest that LA may be safe in the treatment of complicated appendicitis (20–23, 25, 33, 34). Markides' group (2010) (39) performed a systematic review and meta-analysis concluding that LA is advantageous over OA in complicated appendicitis as a result of less surgical site sepsis; however, the level of evidence was confined to retrospective reviews.

In view of the paucity of evidence, I designed a RCT to compare OA to LA in complicated appendicitis.

Chapter 2

Methods

Ethical approval to undertake the study was obtained from the WITS Human Research Ethics Committee, ethics clearance number M110730 (Appendix 1). All participants gave written, informed consent after receiving a verbal explanation of the study together with an information document. The trial was registered on 18/01/12 with Clinical Trials, ISRCTN92257749 (Appendix 2). The Helsinkini Declaration (40) a set of ethical principles regarding human experimentation developed for the medical community by the World Medical Association was adhered to throughout the study.

All patients presenting to the surgical casualty with localized right iliac fossa peritonitis or diffuse abdominal peritonitis suspected to be caused by complicated appendicitis following clinical examination, biochemical tests and radiological investigations were included. Time of onset of symptoms to presentation in casualty was recorded for all patients.

Patients were excluded if they were younger than 12 years of age, had any previous abdominal surgery or were pregnant. Following blinded pathological examination, patients were further excluded if they had either histologically normal or uncomplicated appendicitis.

Randomization into OA or LA was performed by an independent party using an equal (1:1) randomization sequence generated by a computer random number generator software. Sequentially numbered non-transparent envelopes were supplied to the principal investigator. Once the on-call surgeon decided that a patient required an appendicectomy he or she recruited and obtained consent from the patient to be entered into the study. In theatre, after induction of anaesthesia, the patient's randomization status was disclosed by the principal investigator, and the surgeon performed the appropriate procedure. Patients who were randomized but found to have no appendicitis at surgery were excluded from the final

data analysis. The principal investigator was not involved in the management of any potential study patient.

The appendectomies were performed as soon as possible on the hospital's emergency theatre slate. A senior team of consultant surgeons capable of completing both OA and LA performed all the operations. All patients enrolled in the study underwent pre-operative resuscitation, which included antibiotics, according to departmental protocols.

The appendicectomy procedures were standardized in both the groups. OA was either performed through a muscle splitting incision in the right iliac fossa or through a lower midline laparotomy. LA was performed using a three-port technique utilising two 10-mm ports and one 5-mm port. Endopouch retrievers and suction–irrigation devices were used routinely. Intra-abdominal pencil drains were placed if the surgeon was concerned about the appendiceal stump. Wounds were either left open or sutured closed with non-absorbable interrupted sutures at the surgeon's discretion. Specimens were sent for histology and peritoneal fluid for microscopy, culture and sensitivity. The extent of contamination was recorded as either localized to the right iliac fossa, or generalized, extending beyond the right iliac fossa.

All patients received antibiotic therapy, intravenous co-amoxiclavulanic acid 1.2 g eight hourly until the treating physician felt the patient was aseptic. If the patient was allergic to penicillin, they received intravenous ciprofloxacin 500 mg eight hourly. Where necessary antibiotics were changed according to culture sensitivity reports.

Wound sepsis was defined as the presence of wound erythema, calor and dolor with or without a purulent discharge regardless of whether or not the wound had been left open at the initial operation.
Patients were reviewed daily by their operating surgeon until discharge, and again in the out patient department two weeks after discharge for a routine follow-up and feedback of the histology report.

Appendices were recorded as either normal, uncomplicated or complicated. The histological differentiation between uncomplicated and complicated appendicitis was determined using Robbins and Cotrans Pathological Basis of Disease (35) as the presence of acute suppurative appendicitis.

Uncomplicated	**Complicated**
Inflammed appenditis	Acute suppurative appendicitis
	Gangrenous appendicitis
	Perforated appendicitis

Table 3: Histological break down of Uncomplicated and Complicated Appendicitis

The primary outcomes of the study were to compare the following between the OA and LA groups:

1. The intra-operative duration
2. The rates of wound sepsis
3. The number of re-operations
4. The length of hospital stay
5. The rate of re-admissions

Secondary outcomes were to determine whether the duration of the symptoms had any effect on the outcome between the two procedures.

Statistical analysis

Continuous variables were compared between the two groups using the Student's t test or Mann–Whitney U-test, and the Pearson Chi square or Fisher's exact test were used to compare categorical data. A P-value of <0.05 was considered statistically significant. Clinical information captured using Excel and Statistica 10 was used to analyse the data.

Chapter 3

Results

During December 2011 and June 2012, a total of 114 patients met the enrolment criteria, two of which were excluded due to laparoscopic equipment failure. The remaining 112 patients were randomized as shown in Fig. 1. There were 32 male patients in the OA group and 31 males in the LA group. Mean age and pre-operative blood results are shown in Table 1. Table 2 lists the outcome comparisons between the two groups.

The decision to exclude patients with uncomplicated appendicitis or other diagnoses was made following histological assessment by a blinded pathologist. There was minimal discrepancy in the post randomization exclusions between the OA and LA groups which was not statistically significant (P = 0.063).

All patients underwent appendicectomy alone, no right hemicolectomies were performed. No patient in either group suffered an iatrogenic injury such as a bowel or bladder perforation. There were no appendiceal stump leaks. No deaths occurred in the study.

Procedure time

Mean procedure time (±SD) in the OA group was 58.4 (±34.6) min compared to 75.8 (±49.2) min in LA group (P = 0.08).

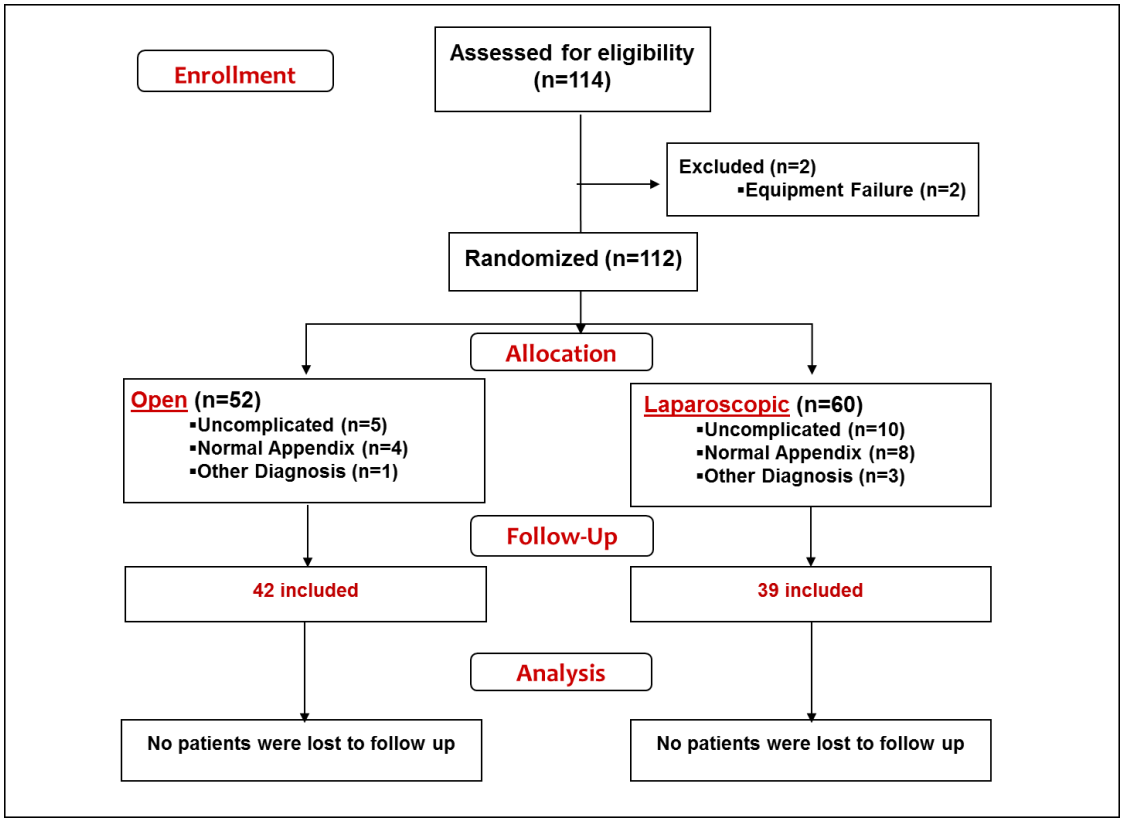

Figure 1: Consort diagram

	Mean Open (SD)	Mean Laparoscopic (SD)	P-value
Age (yrs)	26.6 (13.7)	26.4 (11.25)	0.71
pH	7.38 (0.07)	7.38 (0.06)	0.89
HCO_3^- (mmol/L)	21.7 (2.63)	21.6 (2.69)	0.93
Hb (g/dL)	15.4 (2.27)	14.4 (2.60)	0.09
BE (mmol/L)	-1.9 (2.43)	-2.1 (2.00)	0.53
Lactate (mmol/L)	1.6 (0.59)	2.2 (2.03)	0.60
WCC (109/L)	13.5 (4.61)	14.8 (5.17)	0.21
CRP (mg/L)	**117.0 (116.55)**	**180.9 (135.17)**	**0.04**
CO_2 (mmol/L)	20.9 (2.9)	21.2 (3.3)	0.40
Urea (mmol/L)	4.8 (2.16)	4.6 (2.32)	0.42
Creatinine (µmol/L)	73.1 (19.38)	79.9 (43.12)	0.95

Table 1: Study participant baseline characteristics

	Open	Laparoscopic	P-value
Primary Outcome:			
Intra-operative times (mins)	58.4	75.8	0.08
Wound sepsis (n)	9	2	**0.03**
Re-operations (n)	5	5	0.58
Days of Hospitalization (mean value)	4.5 (1-18)	5.0 (1-15)	0.26
Re-admission	4	3	0.77
Secondary Outcomes:			
Patients presenting within 72 hours	31	25	0.16
Generalized contamination	7	11	0.31

Table 2: Outcome measures

Septic complications

A total of 11 wounds became septic of which nine were in the OA group and two in the LA group (P = 0.03). In the OA group, seven were closed with interrupted nonabsorbable sutures and two were left open; all port sites in the LA group were closed with subcutaneous absorbable sutures. A total of 10 patients required re-operation, three were planned at the time of initial surgery (OA = 2 vs LA = 1), six as a result of septic complications (OA = 2 vs LA = 4) and one patient who had wound dehiscence in the open group. Of the seven patients that required readmission, three underwent re-operation (OA = 1 vs LA = 2 P = 0.37). The remaining five patients had wound sepsis and were treated conservatively.

Post-operative collections were defined as septic collections resulting in systemic sequelae requiring further interventions. Post-operative collections developed in one patient in the OA group and in four of the LA group (P = 0.16). One of the patients in the LA group was treated via percutaneous pigtail drainage and the remaining patients, including the patient in the OA group, were re-operated.

Operative conversions

Three patients in the LA group were converted to an open procedure. In the OA group, 33 patients had McBurney's incisions with a muscle-splitting technique and nine had lower midline laparotomy. There were two conversions in the LA group at the time of initial surgery, one as a result of generalized ileus and the second as a result of an appendiceal mass. Three further conversions took place at reoperation for unresolving sepsis as a result of generalized ileus preventing adequate visualization and washout of the abdomen. Lower midline laparotomy was the surgical approach for all converted cases.

Time to presentation

Patients presenting within 72 h had a significantly greater risk of developing wound sepsis if they were treated with an OA compared to LA (P = 0.014). Patients with generalized contamination had a significantly higher mean CRP (231 vs 152 mg/l, P = 0.02), more post-operative collections (3 vs 1, P = 0.04) and a greater length of stay (6.7 vs 4.9 days, P = 0.03) when compared to those with local

contamination. The numbers of drains used was similar in the two groups with 12 in the OA group and 13 in the LA group.

Uneventful recoveries were made by 32 and 29 patients in the OA and LA groups, respectively. Both the groups had 10 patients that complicated with either wound sepsis or post-operative collections resulting in either re operations, re-admissions or both.

Chapter 4

Discussion

The exact incidence of appendicitis is not known in South Africa. Complicated appendicitis is prevalent as a result of poor health-seeking behaviour, poor referral infrastructure and the influence of traditional medicine (36). Kong et al. (41) found complicated appendicitis to be more prevalent in rural South African patients. For the reasons above, complicated appendicitis is a commonly encountered surgical emergency in South Africa and seeking the ideal operative approach motivated this trial.

The procedure time was a measure of the true operative time or cutting time. The time for theatre preparation, setup and anaesthetic time were excluded. It was however noticed that theatre preparation and setup times were prolonged in the LA group, but this improved as the study progressed. This can be attributed to both anaesthetic and nursing staff becoming accustomed to emergency laparoscopic surgery. Multiple previous studies have quoted procedure duration being longer in the LA group (9, 16–18, 21–23, 37, 38), which was also the case in our study; however, it was not statistically significant (P = 0.08). If I compared the LA and OA operative duration with regard to the extent of contamination, measured as either localized contamination or generalized contamination, the operative duration was the same (70.0 vs. 70.1 min respectively), suggesting that the degree of contamination did not affect the duration of the operation.

The overall conversion rate in this study, two at primary surgery and three at re-operation, was 7 %. Randomized control trials comparing LA to OA (20–23, 25, 32, 33) that have included complicated appendicitis cases reported conversion rates ranging from 0 to 16 %.Hence, the conversion rate is lower than most other studies. A single post-operative collection developed in the OA group and four in the LA group, but this was not statistically significant. One of the patients in the LA group was treated via percutaneous pigtail drainage and the remaining patients, as well as the single patient in the OA group,

were subjected to re-operation. It is our Department's policy to aggressively treat early post-operative sepsis in appendicitis; hence our surgeons have a low threshold for repeat operation in these patients.

A limitation of this study is its sample size. During the planning of the study, a power analysis determined that 1,196 patients would have to be randomized based on a wound sepsis rate of 10 % and a power of 90%. Before embarking on a study of this magnitude, a proof of concept study was decided upon to determine the safety of LA in complicated appendicitis. I did not perform a cost benefit analysis; however in the literature the cost between OA and LA is similar (42).

Data describing the total duration of antibiotic therapy between the OA and LA groups is not available. Our Department's antibiotic policy is to continue post-operative intravenous antibiotics in patients with complicated appendicitis until there is clear evidence that their sepsis has settled, whereupon they are converted to oral antibiotics for a length of time that is determined by the surgeon looking after the patient, but no less than 5 days in total. I acknowledge that the duration of antibiotic therapy is important in treating complicated appendicitis and the lack of duration of data on the antibiotic therapy in our study may have affected our conclusions.

Conclusion

In conclusion, LA is at least as safe as OA for complicated appendicitis. Larger RCT's are required to determine whether or not LA is truly associated with significantly fewer complications and shorter hospital stay.

Chapter 5

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Appendicectomy: Outcomes and Costs of a Case-Control Prospective Single-Operator Study of 112 Unselected Consecutive Cases of Complicated Acute Appendicitis. J Am Coll Surg 218:51-65

Appendix 1: Copy of ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr John-Edwin Thomson

CLEARANCE CERTIFICATE	M110730
PROJECT	Laparoscopic versus Open Procedure for Perforated Appendix: A Randomized Controlled Trial
INVESTIGATORS	Dr John-Edwin Thomson.
DEPARTMENT	Division of Surgery
DATE CONSIDERED	29/07/2011
M1107300DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 27/09/2011 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Martin Brand

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix 2: Copy of Trial Registration

Laparoscopic versus open appendicectomy

ISRCTN	ISRCTN92257749
ClinicalTrials.gov identifier	
Public title	Laparoscopic versus open appendicectomy
Scientific title	Laparoscopic versus open procedure for perforated appendix: a randomized controlled trial
Acronym	N/A
Serial number at source	N/A
Study hypothesis	In the treatment of perforated appendicitis, laparoscopic appendicetomy is associated with lower morbidity than open appendicetomy.
Lay summary	Background and study aims Appendicitis is a painful swelling of the appendix, a finger-like pouch connected to the large intestine. It is traditionally classified as uncomplicated or complicated, and is treated by removal of the appendix, known as an appendicectomy or appendicectomy, which is the most commonly performed surgical procedure. Appendicectomy can be performed by one of two methods. Laparoscopic appendicectomy (LA) involves making several small cuts in your abdomen through which special surgical instruments are inserted. Open appendicectomy (OA) involves making a single larger cut in the abdomen. Currently the Department of Surgery at Chris Hani Baragwanath Hospital, Johannesburg, South Africa, practises both OA and LA in the treatment of perforated appendicitis (burst appendix). To date there have been no studies comparing outcomes between OA and LA in perforated appendicitis. The aim of this study is to compare the intra-operative duration, the rate of wound sepsis, the rate of relook, the length of hospital stay and the rate of re-admissions between the OA and LA groups. Additionally we aim to look at whether the duration of the symptoms has any effect on the outcome between the two procedures. Who can participate? Patients presenting with acute abdomens suspected to be caused by perforated appendicitis at Chris Hani Baragwanath Hospital. What does the study involve? Participants will be randomly allocated to undergo either OA or LA. A team of senior surgeons capable of doing both OA and LA will perform the surgery. Surgeons will perform standardized procedures in both subgroups as per current clinical guidelines. What are the possible benefits and risks of participating? As this study will be comparing the outcomes of two different emergency surgical procedures, patients will be subjected to the risks which are associated with the surgical procedures. It must be noted that all patients recruited into the study need emergency surgery and thus inclusion in the study per se adds no additional risk factors to patients. Where is the study run from? Chris Hani Baragwanath Hospital, Johannesburg, South Africa. When is the study starting and how long is it expected to run for? The study began in December 2011 and ran for about 6 months. Who is funding the study? There is no sponsor for the above trial. Should any minor costs be incurred they will be funded by the Department of Surgery, University of Witwatersrand, Johannesburg, South Africa. Who is the main contact? Dr John Thomson drjohnthomson@gmail.com

Ethics approval	Human Research Medical Ethics Committee, University of the Witwatersrand, Johannesburg, 27/11/2011, ref: M110730
Study design	Prospective single-centre randomized controlled trial
Countries of recruitment	South Africa
Disease/condition/study domain	Appendicitis
Participants - inclusion criteria	All potential patients presenting with appendicitis at Chris Hani Baragwanath Hospital, Johannesburg, South Africa
Participants - exclusion criteria	1. Patients less than 12 years of age 2. Those who have undergone previous abdominal surgery 3. Pregnant patients
Anticipated start date	05/12/2011
Anticipated end date	31/05/2012
Status of trial	Completed
Patient information material	Not available in web format, please use the conatct details below to request a patient information sheet
Target number of participants	100 patients
Interventions	Open appendicetomy (OA) versus laparoscopic appendicetomy (LA)
Primary outcome measure(s)	1. Intra-operative duration 2. The rate of wound sepsis 3. The rate of re-look (the number of re-operations required as a result of the appendicitis or subsequent sequel of the appendicitis) 4. The length of hospital stay 5. The rate of re-admissions
Secondary outcome measure(s)	Whether the duration of the symptoms has any effect on the outcome between the two procedures
Sources of funding	Department of Surgery, University of Witwatersrand (South Africa)
Trial website	
Publications	2014 results in: http://www.ncbi.nlm.nih.gov/pubmed/25318368
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Zip/Postcode	1609
Country	South Africa
Sponsor	University of Witwatersrand (South Africa)
Address	c/o Prof Thifheli Luvhengo Department of Surgery

	Baragwanath Hospital R68 Old Potchefstroom Road PO Bertsham
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Sponsor website	http://www.wits.ac.za/

Date applied	04/12/2011
Last edited	28/10/2014
Date ISRCTN assigned	18/01/2012

Appendix 3



11/8/2014 Gmail - Surgical Endoscopy - Decision on Manuscript ID SEND-14-0772.R1

Gmail by Google

John Thomson <drjohnthomson@gmail.com>

Surgical Endoscopy - Decision on Manuscript ID SEND-14-0772.R1

1 message

angellus_2000@yahoo.co.uk <angellus_2000@yahoo.co.uk> Wed, Sep 10, 2014 at 11:51 AM
To: drjohnthomson@gmail.com
Cc: surgendosc@optonline.net

10-Sep-2014

Dear Dr. Thomson:

On behalf of the Editorial Board I am pleased to inform you that your revised manuscript "Laparoscopic versus open surgery for complicated appendicitis: a randomized controlled trial to prove safety" has been accepted for publication in Surgical Endoscopy.

Questions about your manuscript from now on can best be answered by Raymond Ramonas in the Journal Production Department at Raymond.Ramonas@springer.com.

With kind regards,

Prof. Alfred Cuschieri
Editor-in-Chief, Surgical Endoscopy
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