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Master in Minimally Invasive and Robotic Pediatric Surgery

CHILDREN'S HEALTH RELATED QUALITY OF LIFE AS THE MAIN OUTCOME IN MINIMALLY INVASIVE PEDIATRIC SURGERY. COST-UTILITY ANALYSIS OF LAPAROSCOPIC VERSUS OPEN APPENDECTOMY IN CHILDREN

Supervisor:
Jaume Margarit Mallol

Co-supervisor:
Erick Ardela Díez

Submitted by:
Sara Fuentes Carretero
Matricola: 0000954560

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ABBREVIATIONS

AA	acute appendicitis
CBA	cost-benefit analysis
CEA	cost-effectiveness analysis
CMA	cost-minimization analysis
CUA	cost-utility analysis
ETI	endotracheal intubation
HRQoL	health-related quality of life
ICER	incremental cost effectiveness ratio
LAp	laparoscopic appendectomy
lpm	liters per minute
MCS	Monte Carlo simulation
MIS	minimally invasive surgery
OAp	open appendectomy
QALY	quality adjusted life year
QALM	quality adjusted life month
QoL	quality of life
SD	standard deviation
MIN	minimum value
MAX	maximum value

SUMMARY

Introduction: Economic evaluation in healthcare is becoming increasingly important. Laparoscopic appendectomy is one of the most frequent minimally invasive procedures in pediatric population. By proving its cost-utility in terms of health-related quality of life (HRQoL), we will help to justify the increase in costs of this approach.

Objective: To perform a cost-utility analysis (CUA) between open and laparoscopic appendectomy (OAp and LAp).

Material and methods: A decision analytic model was designed to calculate the cost-effectiveness of LAp versus OAp. We included the data of children operated of acute non-complicated appendicitis that accepted to collaborate answering to a validated quality of life questionnaire. Costs were calculated for each patient. We decided on establish 20,000 to 30,000 euros per quality adjusted life year (QALY) as threshold for cost-effectiveness (λ).

Results: A total of 53 patients were included. Overall mean costs in the OAp were 758.98 € and in the LAp 1,525.50 €. The incremental cost-effectiveness ratio (ICER) was 18,000 euros/QALY.

Discussion: Economical evaluation studies in Pediatric Surgery are scarce and rarely measure outcomes in terms of quality of life. This information is important in the decision making process. Our results encourage the use of laparoscopy in pediatric appendectomy to improve HRQoL of our patients.

BACKGROUND

Health Economics is a trending topic. There is an increasing interest in economical studies in health care with more than 6,000 papers published on this topic in 2019[1]. This is probably due to a widespread awareness of the economic perspective of medicine among the healthcare professionals.

The traditional view of a physician when a medical intervention is introduced is to evaluate the outcomes in terms of efficacy and complications. We would contrast and compare two drugs or two surgical techniques trying to understand which one is better, which one has better resolution rate with less complications or less hospital stay. Obviously, this is absolutely essential. However, we should go beyond and see the wider picture. Once our intervention has proven to be better in terms of efficacy we should study the rest of its implications. The medical community should be aware of the need of taking into account the costs of each intervention in an environment of scarce means and especially in times of economical crisis. When the standard intervention is widely accepted and it has already good results, it may be difficult to prove better outcomes with a new one. In certain cases, there is not enough strong evidence favoring one new intervention over the standard of care, especially when there is a reduced number of patients and the differences we want to detect are small. This is sometimes the case in Pediatric Surgery.

Economics as a science, investigates the best possible way to allocate a resource, as they are limited and could have many alternative uses[2]. This is especially true in Health Economics. (Figure 1)

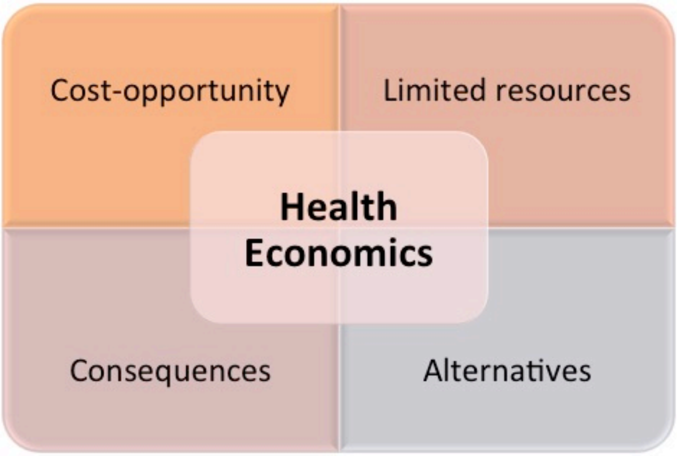

Figure 1: Scheme of Health Economics connecting the main concepts.

Every resource we use in an intervention, regardless it is related to healthcare professionals, equipment or use of spaces, has an opportunity-cost, because we could be using those resources in something else. On the whole, each resource should be destined to its best possible use[3].

Minimally invasive surgery (MIS) was born in an attempt to minimize the surgical trauma on a patient, improving outcomes and recovery after an operation. We have come through a long way from the beginning of the XX century when the first laparoscopes started to be used on animals by means of a pneumoperitoneum[4]. This approach evolved along the century thanks to the arrival of new technological advances, specially the video in the 60's. Gynecologists contributed to its development and the indications spread amongst the different specialties. However, laparoscopy was not widely accepted from the beginning. There were many initial criticisms regarding its use, and it was not until 1989 that the first laparoscopic cholecystectomy was accepted on the Exhibition Hall of the American College of Surgeons meeting. Since then, the revolutionary concept of minimally invasive surgery has widespread in all the different surgical specialties including Pediatric Surgery[5].

Considering the advanced technology and the increased operational times that MIS procedures might require, they have some undeniable increase in costs[6, 7]. There is evidence in adult population that the decrease in hospital stay and the earlier return to normal activity compensate the increase in costs when the results are taken into account from a social and health system perspective[8]. MIS has proven its superiority to traditional open surgery in adults in procedures such as cholecystectomy, appendectomy or colon surgery[9,10,11].

However, the particularities of the pediatric patient make sometimes difficult to justify the use of MIS for many reasons. First of all, most of the procedures are done on a day-case surgery basis and even in the case of acute non-complicate appendicitis, children are discharged shortly after the surgery and the recovery of a previously healthy child after open appendectomy is most of the times short and uneventful. When a dedicated Pediatric Surgery team takes care of pediatric surgical conditions, and protocols and enhanced recovery pathways are implemented, outcomes are excellent for the majority of elective cases and improving them becomes a challenge[12]. In addition, obesity, one of the added conditions in which MIS is clearly an advantage, is far less frequent in children than in adults, being open surgery easier and faster in small and thin patients[13]. Lastly, complex and longer procedures are not as numerous as day-surgery cases, therefore it is difficult both to complete a learning curve in advanced pediatric MIS to ensure best results and to have enough number of cases to reach high quality evidence on the benefits of this approach[14].

In spite of these difficulties, in recent years there have been an increasing number of publications presenting large series of cases with long-term follow-up of different pediatric MIS procedures showing its feasibility and safety. This is the case for esophageal atresia, congenital diaphragmatic hernia and or fundoplication for instance[15,16,17]. Moreover, randomized controlled trials have been carried out successfully in the most prevalent conditions like acute appendicitis, inguinal hernia and piloromiotomy, showing positive results in terms of outcomes and complications favoring the minimally invasive approach[18,19,20].

There are not many studies regarding the economical evaluation of pediatric MIS. Most of them are focused on comparing the costs of the laparoscopic procedure and the costs of the postoperative course or hospital stay without taking into account quality of life measurements[21,22].

It is important for healthcare professionals to understand the differences in methodology of these kinds of studies, to analyze the data and assess the implications of our choices in the best possible way.

Drummond and cols defined economic evaluation in healthcare as "*comparative analysis of alternative courses of action in terms of both their costs and consequences*"[23]. In our case, we do so by evaluating cost-opportunity and health effects (consequences) of two different surgical approaches (open and laparoscopic).

On the one hand, costs can be divided into three different categories:

- Direct costs: they are the ones directly derived from the intervention. They can be further divided into direct healthcare costs (such as hospital stay) and direct non-healthcare costs (such as transport to the hospital).

- Indirect costs: those are the ones related to the loss of productivity of the patient or in case of children, of the parents or caregivers.

- Intangible costs: they are related to psychological impact, or pain. They are subjective and therefore not usually considered in economic studies as they cannot be easily measured.

On the other hand, consequences can be measured in different ways, defining different approaches to the economical analysis.

There are four different ways to undertake this analysis depending on how the health effects or consequences are measured[3]. (Figure 2)

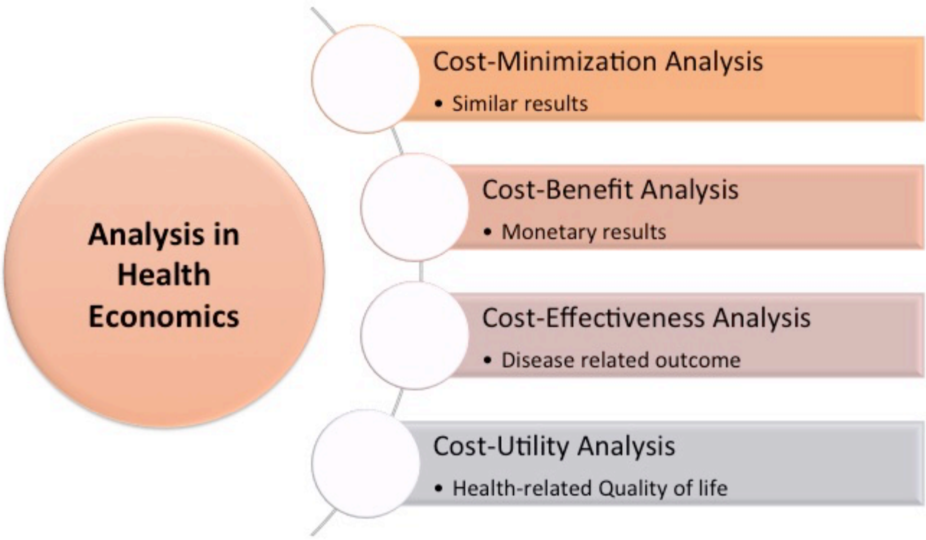

Figure 2: Different types of health economic studies.

First of all we have the cost-minimization analyses (CMA). In this type of study we assume that the two approaches have similar results therefore we are looking to solely minimize the costs. Regarding pediatric MIS it would not be appropriate as there is already evidence that there could be better outcomes with the laparoscopic approach and we would be willing to assume an increase in costs if it is worth.

Secondly, cost-benefit analysis (CBA) measures the health effects in monetary terms. Although they are useful from the provider's perspective, neither this kind of study nor the CMA are the preferred for pediatric MIS. We look for the wellbeing of our patients both physical and psychological, in terms of efficacy and complications but also satisfaction with their scars, functional outcome, and so on and this could not be measured in monetary terms.

The cost-effective analysis (CEA) measures the health effect in terms of a physical outcome, general or disease-specific. The most common unit is life-years gained. In the case of pediatric MIS could be something else, for instance time to full feeds in open versus laparoscopic pyloromiotomy[24]. In this case we are measuring a direct positive consequence or health effect of our intervention that directly benefits the patient.

Finally, one step ahead we have the cost-utility study (CUA). In this analysis we measure the health effects in a way that takes into account not only the health-state but the quality of this health-state as well. This concept is called health-related quality of life (HRQoL). For instance, after appendectomy the health-state will be "cured", but it is not definitely the same a cured child that have some residual discomfort and that takes more time to get back to school or sports or social life, that a child that can do so right away. The unit we use to measure HRQoL is the quality-adjusted life-year or month (QALY or QALM)[25]. This measurement is estimated from the area under the curve of preferences regarding health status over time. (Figure 3)

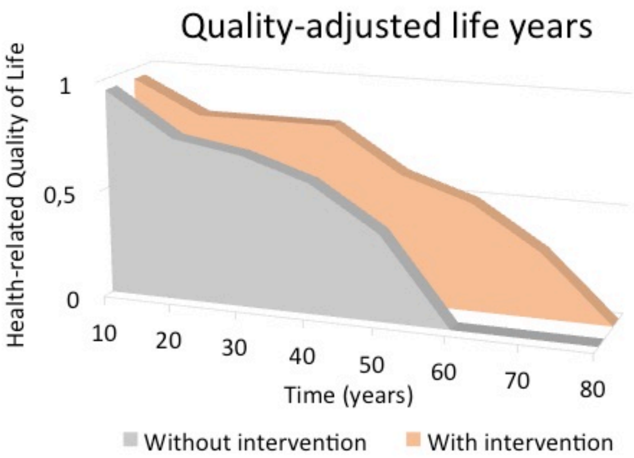

Figure 3. Example of Health-related quality of life in two hypothetical scenarios with and without an intervention.

This curve depicts how we would like our health to be along a period of time, where 0 represents death and 1 the best possible health. QALYS can be obtained by many validated health questionnaires that can be disease specific or generic. There are also quality of life questionnaires specially developed for pediatric population that can be used for this purpose[26].

The main advantage of this measurement is that it takes into account both the quality and the length of life; therefore it overcomes the limitations of some other monetary or disease-specific outcome measurements. QALYs can be compared between different conditions and interventions, as it is a generic measurement of the health effects or consequences.

Summing up, CBA would take into account only monetary measurements, whereas both CEA and CUA would take into account quality of life. The main difference between them is that CEA measures a disease-specific outcome and CUA a generic adjusted quality of life unit. As a consequence CUA results could be compared among different interventions, diseases and conditions.

In order to represent the results in CEA and CUA we use a chart in which X-axis represents health effects and Y-axis represents costs. (Figure 4)

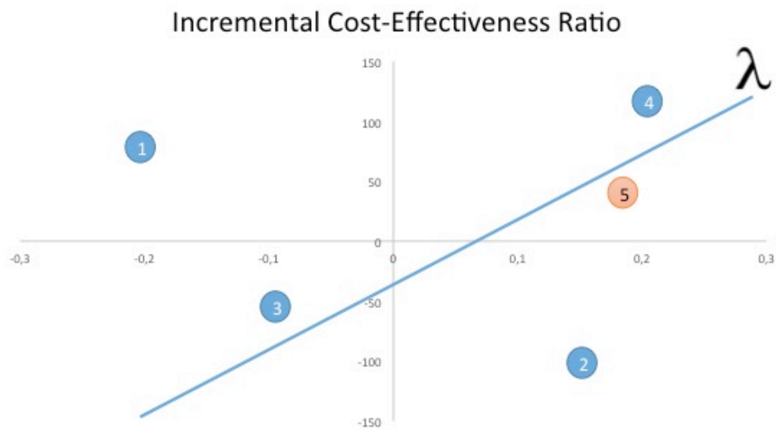

Figure 4: The graphic representation of the incremental cost-effectiveness ratio (ICER) in five different scenarios. In nº 1 the intervention is more expensive and it has less HRQoL. In nº 2 it is less expensive and has associated a better HRQoL. In point nº 3 is less expensive and it has also less HRQoL. In points nº 4 and 5, the intervention is more expensive but it provides better HRQoL. The difference is that nº 4 is over the threshold λ that we establish as the limit of what we would be willing to pay to improve HRQoL, and nº 5 is under it therefore it would be the best choice.

Assuming the traditional surgical technique or gold standard is at point (0,0) the new one would have a variation in both costs and effects and this would be represented in the chart as the incremental cost-effectiveness ratio (ICER) as shown in the following formula:

ICER= Cost A-Cost B/QALY A- QALY B

When the ICER is in the left upper quadrant of the chart on figure 4, the new intervention is obviously worthless and it should not be implemented (it would mean it is more expensive and with less gain in quality of life). On the contrary, when it falls into the right lower quadrant it would be the best possible scenario, less expensive and better results, therefore it would be clearly considered to be implemented. The incertitude emerges when the ICER falls into the right upper quadrant and the left lower one. We would have to establish the threshold of the increase in costs that we would be willing to accept in exchange for an improvement in patient's quality of life (willing-to-pay) usually named λ[27,28].

If the ICER of our technique were situated below the threshold we would accept the new treatment as cost-effective.

ICER= Cost A-Cost B/QALY A-QALY B=Δ Cost Δ QALY≤ λ

Regardless the kind of analysis we chose, it is important to take into consideration the perspective over which we run the study. There are different perspectives that we can adopt for any decision. For instance, the perspective of the provider or the hospital, which would be focused on the duration of the episode of care. The perspective of the patient, on the other hand, would extend even longer. Depending on the perspective that we consider, we will have to calculate the costs and outcomes during a specific timeframe. The perspective of the society is usually considered in most of the studies because it is the most complete in terms of costs[29].

Given the information stated before, we have considered that the best possible approach to undertake the economical evaluation of pediatric MIS procedures is a CUA with the perspective of the society.

Among all the possible procedures we could have chosen to evaluate, we have decided to begin with appendectomy for the following reasons.

Acute appendicitis is the most frequent surgical emergency in children[30]. About 20 to 30% of all children that are referred for evaluation to the pediatric surgeon for acute abdominal pain will turn out to have it[31]. The overall incidence is 5.7–50 per 100,000 inhabitants per year with an overall lifetime risk of 8%[31,32].

Although acute appendicitis can present at any age, it has a peak of incidence between 10 and 18 years old, with a predominance of males[33].

The knowledge about this condition has incredibly increased in the past decades and nowadays both its natural history and its management keeps on generating controversy.

In the classical pathophysiological explanation of its etiology, obstruction of its lumen leads to suppurate inflammation that could progress to perforation, causing either peritonitis or appendix phlegmon or abscess[34]. The mentioned obstruction could be caused by a fecalith, parasites, hyperplasia of lymphatic tissue or a tumor. However, it has been postulated that this mechanism of obstruction may explain only half of the cases. There are some other factors implicated in its etiology, like racial or geographic factors, diet, certain pathogens or even some genetic predisposition with some patients having up to 30% increased risk of developing appendicitis[35].

The traditional belief regarding the natural history towards perforation if untreated is also being revisited. There are reports of resolution without treatment, relapses and even the so-called chronic appendicitis[36,37]. It has been postulated that some specific immunological factors would predispose some children to early perforation whereas some others would be more likely to have a self-limited course[38]. This is the reason why although the traditional approach for acute non-complicated appendicitis is appendectomy, there is a trend in recent years towards non-operative management[39]. It is common practice in many centers to avoid immediate surgery in the case of acute appendicitis when it is complicated with phlegmon or abscess formation. In these cases, a course of antibiotics followed by delayed appendectomy after 6-8 weeks is the standard of care in many Pediatric Surgery centers[40]. In recent years after favorable results in adult population it has been proposed to adopt this strategy even in acute non-complicated appendicitis, with apparently favorable outcomes in published results[41]. The rationale of this approach is some evidence of a possible role of the appendix in the normal homeostasis of intestinal flora or an influence on immunological regulation of the intestinal barrier[42]. Although appendectomy is not clearly associated with any posterior condition that could be develop later in life, it is widely accepted that the appendix has a role to play and it is not completely a vestigial structure.

Regardless all these new trends, until enough strong evidence leads us to a generalized agreement on non-operative management of acute appendicitis, appendectomy remains the first line therapy in most Pediatric Surgery units around the world[43].

As it is one of the most frequents procedures in pediatric population, it is constantly the subject of high quality research, randomized controlled trials and metaanalysis. This is why it provides us with strong evidence, allowing us a more scientific and evidence-based approach[43].

First laparoscopic procedure in a pediatric patient was reported in 1971[44]. Since then, many things have changed and nowadays almost 90% of all appendectomies are minimally invasive[31]. There are many techniques described for laparoscopic appendectomy, including single site surgery, with or without exteriorization of the appendix and even robotic appendectomy. However the most widespread one is the three ports technique. Randomized controlled trials have failed to prove any significant superiority of single site appendectomy over classic three-ports approach, and apparently the cosmetic scores tend to be similar as time passes[45,46].

In the first years, it seemed to be a trend towards an increased risk of postoperative abscess formation in complicated appendectomies but nowadays it is clear that this is not the case. On the contrary, there is a decreased risk of would infection and less pain on the first postoperative day as it is reported in the most recent metaanalysis in Cochran Library[47].

Previous studies have evaluated the different approaches, open and laparoscopic, in terms of cost effectiveness or costs of hospital stay but none has evaluated before in terms of health-related quality of life of patients after surgery[22].

As the last metaanalysis in the Cochrane Library states, CEA and CUA are lacking in pediatric appendectomy and this data should be analyzed as well in order to have the best possible evidence in all aspects, clinical and economical, of minimally invasive surgery for appendicitis in children[47].

OBJECTIVE

The aim of this study is to perform a cost-utility analysis between open and laparoscopic appendectomy in acute non-complicated appendicitis in children to prove the hypothesis that laparoscopic appendectomy is superior in terms of health-related quality of life and cost-effective over open appendectomy.

MATERIAL AND METHODS

1. Type of study and population included.

This is a retrospective analytic economical study type cost-utility.

We have included pediatric patients between 8 and 15 years old diagnosed with acute non-complicated appendicitis operated in two Pediatric Surgical Centers over the period between September 2017 and August 2020.

Criteria to define uncomplicated appendicitis are less than 2 days of symptoms and no clinical or radiological findings of phlegmon, intraabdominal abscess or peritonitis.

The inclusion and exclusion criteria are summarized in table 1.

INCLUSION CRITERIA	**EXCLUSION CRITERIA**
Between 8 and 15 years old	Previous physical condition
Uncomplicated appendicitis	More than 2 days of symptoms
Agreed to participate	Evidence of phlegmon, abscess o peritonitis

Table 1. Inclusion and exclusion criteria of the study population.

2. Protocols for non-complicated appendicitis and details of intervention.

The protocol followed in both centers is the same.

2.1 Treatment at admission.

All patients are admitted with nil-per-oral, intravenous fluids, intravenous analgesics and all of them receive a preoperative prophylactic dose of intravenous amoxicilin-clavulanic acid (gentamicin + metronidazole in case of allergy to beta-lactamases).

2.2 Surgery

Surgery is undertaken within the next hours, when the patient is fasting for at least 6 hours and there is availability of the surgery theatre.

Patients undergo open or laparoscopic surgery depending on surgeon's choice and availability of the equipment.

2.2.1. Laparoscopic Appendectomy

After anesthetic block with bupivacaine and lidocaine, we enter the peritoneal cavity by open technique, positioning the first port (a 11 mm one) through an infraumbilical incision. We purge the tubes first and then connect to the trocar and start insufflation with low flux at 2 litres per minute (lpm) until we reach a maximum pressure of 10-12 mmHg. We use a 5 mm-30º lens. We inspect the peritoneal cavity and then position two additional 5 mm ports at the left iliac fossa and at hypogastric area under direct laparoscopic vision and after infiltration with local anesthetics. Mesoappendix and appendix are dissected with either electrocautery, or endo-sealer depending on the characteristics of each case and surgeon's preference. The appendix is transected by endo-stapler or sectioning between endo-loops. We extract the appendix through the umbilical trocar. We close the fascia with interrupted 2/0 polyglactine stitches at the umbilicus and we close subcutaneous tissue with 3/0 polyglactine stitches in all ports. Skin is closed with interrupted absorbable intradermic 5/0 polyglactine stitches.

2.2.2. Open Appendectomy

For the open technique, after abdominal wall block with bupivacaine and lidocaine, we make a transverse incision at the level of the McBurney point[30]. We keep it as limited as possible. The fascia is opened with scissors and muscles are separated and preserved. Appendix is localized and brought out of the incision with the minimum possible manipulation. Mesoappendix is dissected ligating appendicular vascular branches and appendix is transected between ligatures. The stump is inverted by means of a purse-string suture. We aspirate fluids in the peritoneal cavity when present. We close the incision in layers, with a running 3/0 polyglactine suture in the peritoneum, interrupted 2/0 polyglactine stitches to approximate muscular layers and a running 2/0 polyglactine suture in the fascia. Subcutaneous tissue is approximated by interrupted 3/0 polyglactine suture and skin is closed by means of a running intradermic 5/0 polyglactine absorbable suture.

2.3 Postoperative management

2.3.1 Antibiotics

Antibiotic prophylaxis is discontinued when the appendix turns out to be flemonous. If it has some degree of gangrene or necrosis with purulent intraperitoneal fluid, postoperative antibiotherapy is started with either intravenous cefotaxime plus metronidazole or piperacilin-tazobactam alone for 5 to 7 days (until the child is afebrile, feeding normally and normalization of analytical parameters). In the intermediate cases with some evidence of localized gangrene without purulent fluid a short course of amoxicilin-clavulanic acid plus gentamicin or cefotaxime plus metronidazole is established for 48 hours.

2.3.2 Oral intake

Oral intake is re-established 4-6 hours after surgery and intravenous fluids discontinued before 12 hours unless vomiting appears. Diet is progressed as tolerated.

2.3.3. Postoperative pain

Postoperative pain is controlled with both metamizole scheduled every 6 or 8 hours and acetaminophen alternating for the first 24 hours at standard doses. For the following days only metamizole is scheduled, leaving acetaminophen as rescue. In patients older than 12 years, dexketoprophen is sometimes used as a rescue if needed.

2.3.4 Hospital stay

Patients are discharged when they are tolerating, with good pain control and once the antibiotic course, if needed, has finished. Usually the hospital stay is 1 to 2 days for flemonous appendicitis and 2 to 7 days of gangrenous appendicitis.

3. Decision model

We constructed a decision analytic (Markov) model in order to compare the two approaches[23]. We calculated the probabilities of each branch of the flowchart according to previous published data[47]. We took as reference OAp technique, as the traditional standard of care, and compared the results with those of LAp.

4. Cost estimation

It was decided to include only the direct costs of the interventions[48,49]. Both indirect and intangible costs such as days that the parents did not go to work or psychological impact were not taken into account because of the difficulty to accurately estimate them.

Intraoperative costs, hospital stay and postoperative follow-up appointments were included. Information on costs was provided by the two centers participating on this study.

The intraoperative costs were calculated for each patient including the items listed in table 2.

Item
Laparoscopic Hardware including light source, screen, insufflator and camera
Optics 5 mm 30º
Light cable
Reusable laparoscopic instruments 5 mm
Silicone tubes
Open surgery instruments
Trocar 5 mm

Trocar 11 mm
Polydioxanone ties
Other sutures
Endo-sealer
Endo-stapler

Table 2. Items considered in costs estimation for LAp.

For laparoscopic hardware and reusable instruments, we considered a life span of 10 years. We calculated the mean number of times they are used per year and an equivalent cost was estimated for each patient, dividing the total amount per 10 years (approximate life span) and per patients-per-year.

Regarding operating room consumables, such as maintenance, sterilization of the instruments, anesthetics and so on, we considered them to be similar between both groups, as well as healthcare professionals working on theatre.

We documented analgesics and antibiotics consumption and calculated the prices according to the doses received during hospital stay for each patient.

The price of each day at the hospital was calculated from standard hospital statistics that already include salaries of nurses and staff and other expenses. The total cost of hospital stay was calculated multiplying the day price by the days each patient was at the hospital.

The price of each outpatient visit was considered as well, it was calculated from general hospital statistics and costs.

All costs are presented in Euros (exchange rate 2019).

5. **Health-related quality of life**.

We measured children's quality of life with the validated general questionnaire KIDSCREEN-10. The KIDSCREEN questionnaires are a series of instruments developed and normalized to assess health-related quality of life in children[50]. They are generic, not disease-specific, which means they can be used for different researches, in a variety of conditions and in previously healthy children. There are three versions of the KIDSCREEN questionnaires, with 52, 27 and 10 items (short version)[51,52,53]. They all have been validated in different languages including Spanish[54]. We have chosen the KIDSCREEN-10 because it has been previously reported its extrapolation to QALYs, which is the standard measure of HRQoL[55] in CEA and CUA. (Figure 5)

HRQoL ranges from 0 to 1, being 0 death and 1 perfect health.


KIDSCREEN

KIDSCREEN-10 INDEX

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Figure 5. Cover page of the KIDSCREEN-10 questionnaire in Spanish.

Parents or caregivers were contacted by phone call, asked informed consent and when they accepted to participate, they responded to the questionnaire.

7. **Sensitivity analysis and acceptability curve.**

We followed the principles for reporting results published in the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement extended for non-pharmacological trials[56].

The sensitivity analysis was used to transfer the uncertainty of different estimations to the outcomes of our model, comparing them with different possible values. A probabilistic multivariate sensitivity analysis was done with 5,000 Monte Carlo Simulations (MCS). MCS is a statistical tool that allows us to do stochastic analysis by generating random samples and calculating a result for each of them. We calculated the 95% confidence interval of the results of this sensitivity analysis.

We used a cost-effectiveness plane to show each pair of costs and outcomes of the model.

We established a cost-effectiveness acceptability line to determine the LAp cost-effectiveness to OAp with a reasonable level of willingness-to-pay.

We established a 20,000 to 30,000 euro-per-QALY threshold (λ) for cost-effectiveness as it is widely accepted in literature and it is a frequently used value in many healthcare cost-effectiveness analysis[57].

A 3% discount rate per year was applied for the estimation of costs and QALYs, following current health economic guidelines[58].

We calculated the incremental cost-effectiveness ratio (ICER) of LAp in relation with OAp. If the ICER of LAp were not to exceed the threshold limit established it would be considered cost-effective.

Although we consider that the perspective of the society it is the most appropriate because it takes into account all aspects of the medical intervention[29], we decided to undertake our analysis under the perspective of the health-provider due to the difficulties to estimate the social costs of the condition.

8. **General statistics**

For statistical analysis, we used the IBM SPSS Statistics version 23.0 (IBM Corporation, Armonk, NY)

In order to compare the two study groups, we performed a statistical analysis for independent samples. We run a Kolmogorov-Smirnov test for each variable to check for normality. We compared basal characteristics of both groups.

For general descriptive statistics, quantitative data are expressed as mean and standard deviation or median and minimum and maximum values in variables that do not follow normal distribution. Categorical data are expressed as frequencies with percentage (%).

Non-parametric test were used for analysis. Continuous data were assessed with Mann-Whitney U tests. Multivariable linear regression models were developed using the Spearman test.

A p value of less than 0.05 was considered statistically significant.

RESULTS

Fifty-three patients meet the inclusion criteria and agreed to participate answering to the KIDSCREEN-10 questionnaire.

None of the data gathered followed a normal distribution according to the results of the Kolmogorov-Smirnov test.

There were 37 (69.8%) boys and 16 (30.2%) girls. Age ranged between 8 and 14 years old with a median of 10 years. At the time of surgery, in 77.4% of the cases, the appendix was macroscopically flemonous and in 22.6% it was gangrenous. Regarding the approach, there were 27 OAp and 26 LAp. Characteristics of each group are summarized in table 3.

	OAp	LAp	Total
n	27	26	53
Gender			
Male	19	18	37
Female	8	8	16
Median Age (min-max)	10 (8-13)	12 (8-14)	10 (8-14)
Type of appendix at surgery			
Flemonous	20	21	41
Gangrenous	7	5	12
Median hosp. stay (min-max)	1 (1-6)	2 (1-5)	2 (1-6)
Complications			
Wound infection	0	0	0

Intra-abdominal abscess	0	0	0

Table 3. Demographic and general data.

Both groups OAp and LAp were homogeneous without differences in gender and type of appendicitis. The median age was lower in the OAp group (10 vs. 12) being this difference statistically significant (p=0.008) (figure 6).

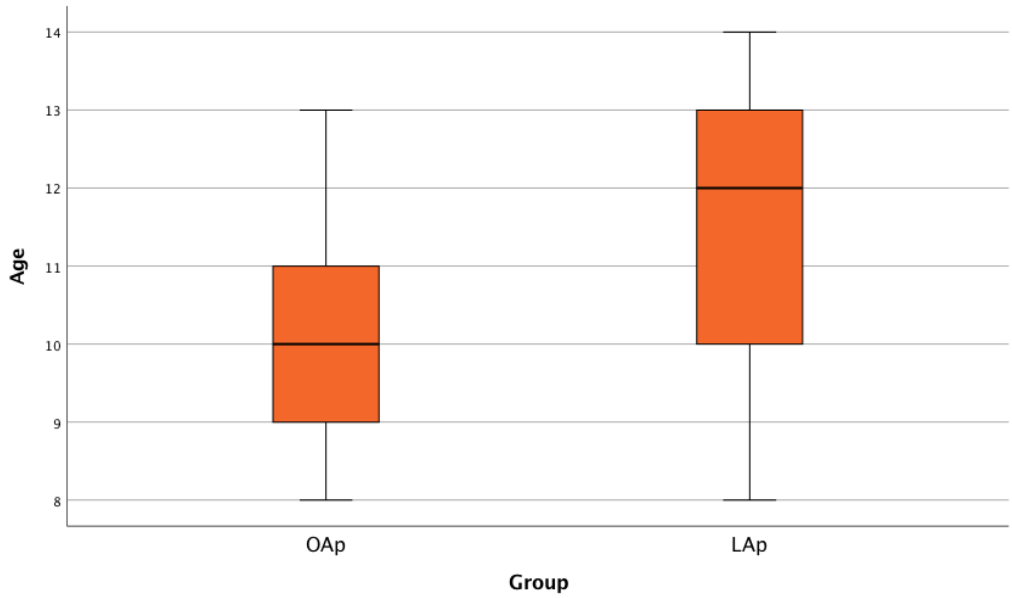

Figure 6. Box plot showing differences in age between the two groups.

We did not detect any significant difference in hospital stay. The median value in the OAp group was 1 and in the LAp 2. In both groups the hospital stay for flemonous appendicitis was between 1 and 3 days (most of them 2 days) and for gangrenous appendicitis 3 to 6 days (most frequent value 2 days).

There were no complications in any group.

The cost of each item considered in the estimation is summarized in table 4.

LIST OF COSTS

Item	Price (in euros)
Laparoscopic Hardware (amortization per patient)	**18.88**
Optics 5 mm (amortization per patient)	**2.30**
Light cable (amortization per patient)	**1.13**
Laparoscopic instruments 5 mm (amortization per patient)	**5.8**
Silicone tubes (amortization per patient)	**0.21**
Open surgery instruments (amortization per patient)	**1.6**
Trocar 5 mm (x2)	**58.54 (117.08)**
Trocar 11 mm	**46.43**
Polydioxanone ties (x2)	**13.17 (26.34)**
Other sutures	**12.72**
Endo-sealer	**702**
Endo-stapler	**399**
Hospital Stay per day	**323.28**
Intravenous fluids 500 cc	**0.88**
Acetaminophen per dose	**0.52**
Metamizol per dose	**0.51**
Dexketoprofen per dose	**0.26**
Amoxicilin-clavulanic per dose	**0.95**
Metronidazol per dose	**0.58**
Cefotaxime per dose	**0.6**
Piperacilin-tazobactam per dose	**2.26**

Gentamicin 40 mg	**0.58**
Gentamicin 240 mg	**2.09**
Postoperative follow up outpatient visit	**72.34**

Table 4. Costs per item

The costs of LAp ranged from 685.53 to 2082.53 euros with a median value of 1711.25 euros for patient, considering the items mentioned in table 4. This range is explained by the use or not of the endo-sealer or the endo-stappler and the length of hospital stay. The costs for OAp ranged between 465.03 to 2122.99 euros with a median value of 465.91 euros. These variations depended only on hospital stay, with an outlier value of 2122.99 euros due to a hospital stay of 6 days in one patient. LAp represented an increase in costs with a difference between the median values of 1245.34 euros. This difference is statistically significant (p<0.001) (figure 7)

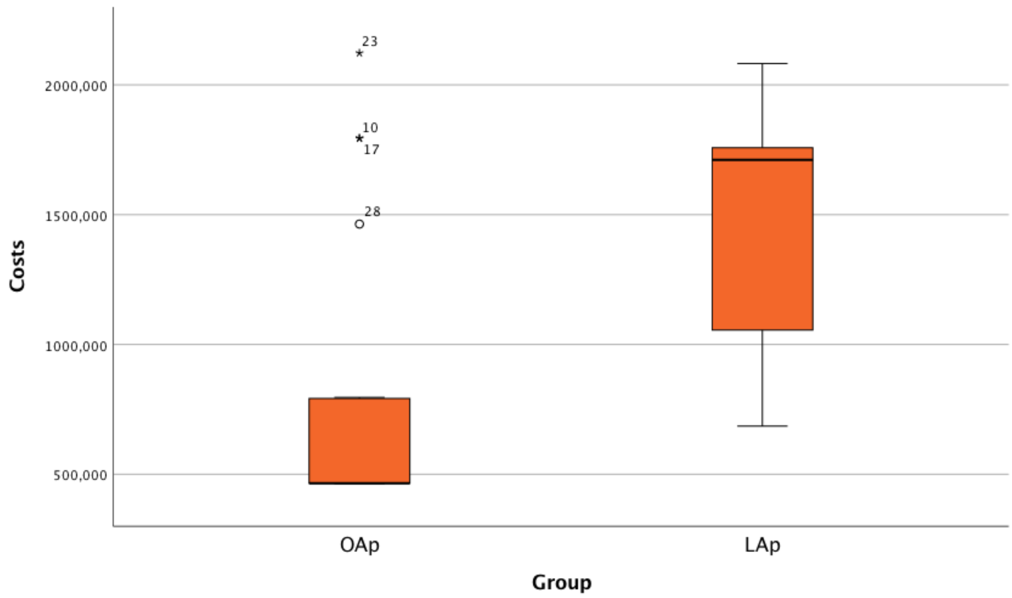

Figure 7: Box plot showing differences in costs between the two groups.

Regarding the KIDSCREEN questionnaire results, patients from the OAp group scored better in one general item related to emotional wellbeing. Whereas in the LAp group, scores were significantly better in items related to the specific areas of relationship with friends and family and in those related to performance and getting back to school. In the rest of items there were no statistically significant differences.

When considering the QALYs, the median value in the OAp group was 0.75 (0.67-0.82) and in the LAp group 0.77 (0.66-0.88), without reaching this difference statistical significance (p=0.816) (figure 8)

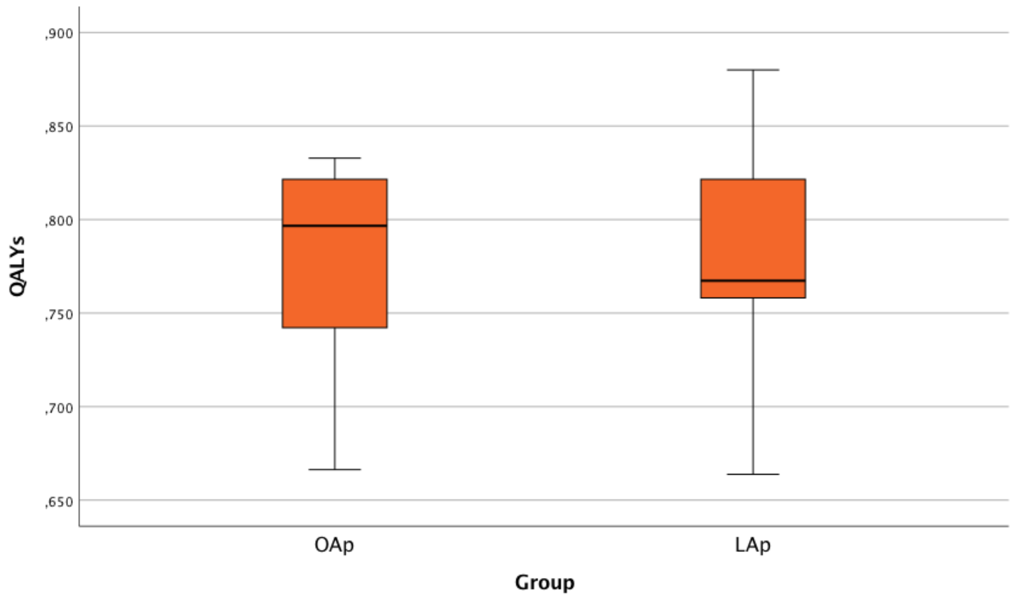

Figure 8: Box plot showing the distribution of QALYs in each group

The multivariate analysis considering the rest of the variables apart from the group LAp or OAp showed no significant correlation with QALYs.

The results of the cost-utility analysis are summarized in table 5.

	OAp (n=27)			LAp (n=26)		
	Mean (€)	Confidence Interval 95%		Mean (€)	Confidence Interval 95%	
		Lower	Upper		Lower	Upper
Costs (€)						
Mean Total Cost	758.98 €	572.09 €	945.88 €	1,525.50 €	1,353.66 €	1,697.34 €
Utility						
QALYs	0.73905867	0.72490661	0.75321072	0.781354346	0.759565399	0.803143294
Incremental Results						
Incremental Cost (€)	---	---	---	766.51 €	751.46 €	781.57 €
Incremental Utility (Qaly)	---	---	---	0.042295679	0.04993257	0.034658789
ICER (€/Qaly)	---	---	---	18,122.73 €	15,049.51 €	22,550.30 €

Table 5. Summary of the cost-utility analysis.

The acceptability curve for LAp over OAp, represents the probability that LAp is cost-effective according to the values that we set as threshold for willingness to pay. Here we can se where our threshold of 20,000 to 30,000 euros/QALYs is located. (Figure 9)

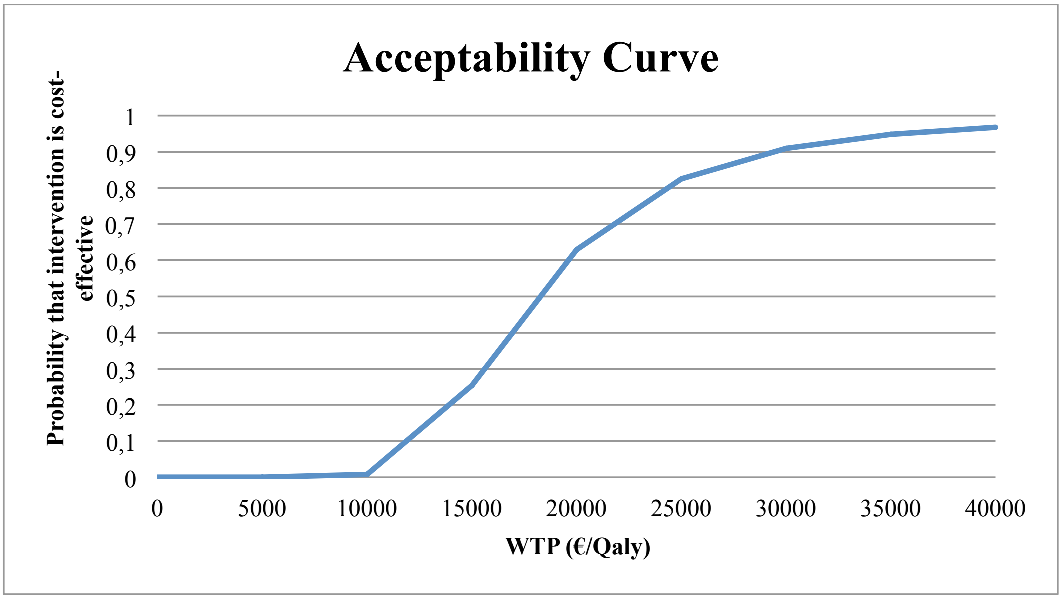

Figure 9: Acceptability curve. (WTP = willingness to pay)

The incremental cost-effectiveness ratio of choosing LAp over OAp was 18,122.73 euros/QALY, which is just below of the established cost-effectiveness threshold λ set at 20,000 to 30,000 euros/QALY.

In figure 10 we can see the graphical representation of the probabilistic simulations generated to prove our model. As it is depicted in the figure, most of the simulations are under the threshold of cost-effectiveness.

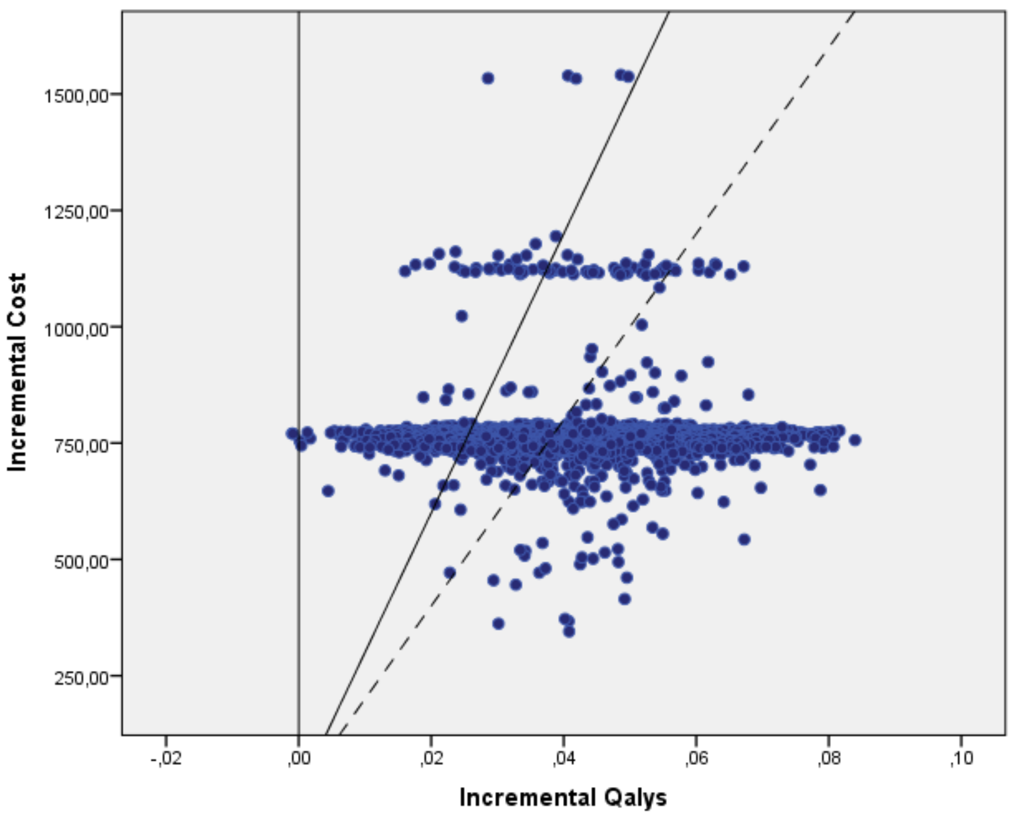

Figure 10. Incremental cost-effectiveness plane. The continuous line is the threshold λ of 20,000 euro /QALY and the dotted line is the 30,000 euro/QALY one.

DISCUSION

Surgery as a whole is much more than the single act that takes place in the surgery theatre. From the indication of the intervention at the outpatient visit or at the ER to the surgery theatre and beyond during the follow up. This is especially true in children, in which the implications and the consequences in the future, may be even more important than in the adult patient. Response to stress, psychological impact, and particularities of anesthetics in the pediatric patient are all examples of how the surgical procedure on a child is complex and delicate. It is also essential to take into account the role of the team-work around the surgical procedure. Nurses, anesthetists and pediatricians are all implicated in the care of the surgical patient along with the surgeon. And in all this net of interactions, there is also a place for the social perspective, the economic aspects and the responsibility of using wisely the available resources when they are limited as in a public healthcare system. (Figure 11)

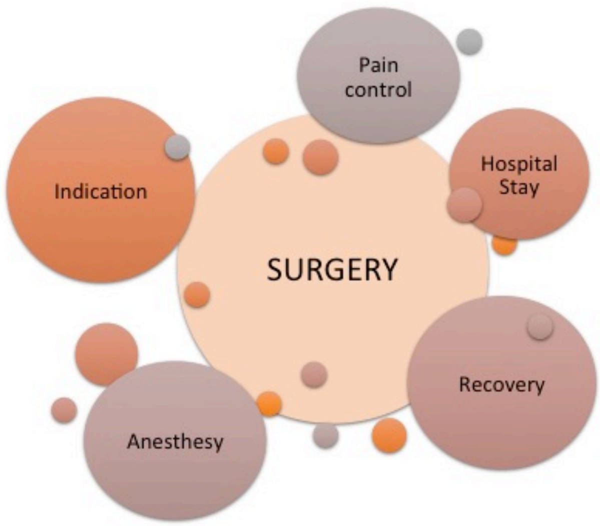

Figure 11: Representation of different aspects of the surgical intervention.

If we want pediatric MIS to evolve and take the place that it deserves amongst all the Pediatric Surgery centers, especially small centers such as ours, we have a commitment to prove its less invasiveness in all aspects and especially that what it costs is worth, not in monetary terms, but in quality of life of our patients.

All the achievements that have led to the present development of MIS have been progressive and have involved different areas. Besides technical advancements, a favorable and supportive environment is needed. Both the society and the policy makers have to be convinced not only of its safety and efficacy, but also of its cost-effectiveness.

This is why the economic analysis of healthcare is important not only for the provider and governmental policy makers, but also for surgeons, all health-care professionals and even for patients.

In addition, when an economic study is well designed, it can also serve for the decision-making process of all the professionals implicated in the care of a child. This is also one reason for which surgeons should be more implicated in the development of the decision analysis tree of economic health studies. Decision analysis could be defined as the process of making a calculated and balanced choice under circumstances of incertainty[23].

The decision analytic model is both useful and easy to work with, once we have come familiar with the general concepts. (Figure 12)

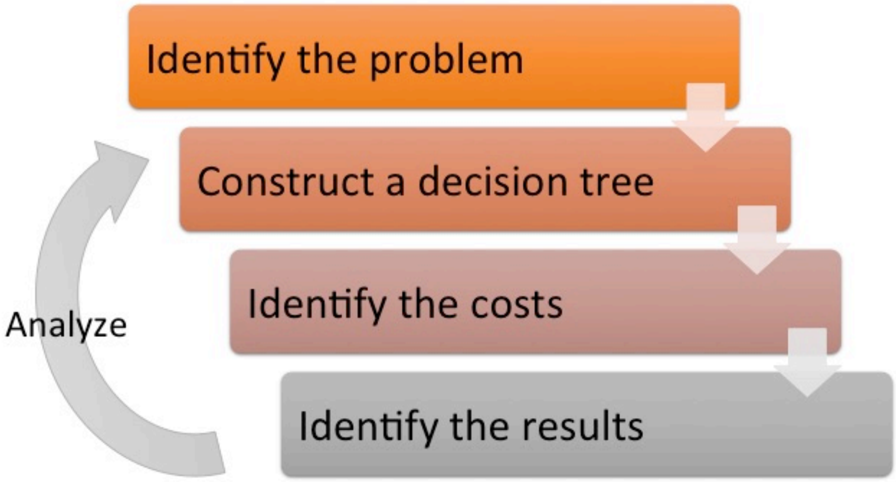

Figure 12: Steps to take to make the decision analytic model.

Our decision analysis tree was very simple, as we were focusing on postoperative HRQoL. We did not design it to help us to choose one option or another, as it was a retrospective study, and we could not complete it with our data as we did not have any patient with complications. However, if we could detail even more the patient characteristics and the outcomes of each technique on specific cases, such as obese patients, or female patients with possibilities of ovarian conditions for instance, the decision analysis tree could help us to choose the best possible option for each particular case considering the probabilities of outcomes in each branch. For instance, when considering the non-operative management of acute appendicitis, a well-designed decision analytic model that considers the different outcomes regarding recurrence, rates of failure of antibiotic treatment or complications of initial surgery could help us to decide the best possible option considering each specific patient[59].

Once the decision analysis tree has ben designed, the economical study should proceed ideally in a prospective way. In our case, we decided to design our study retrospectively because there is no any other study regarding HRQoL in pediatric MIS and we wanted to have a pilot experience to explore general data and to determine on what to build our future research.

One of the drawbacks that we found when designing our study was the lack of instruments to assess the HRQoL in the surgical pediatric patient and the difficulties when trying to apply them to clinical research[60]. There are some instruments designed for specific conditions such as pediatric cancer or diabetes but it is not easy to find any general instrument for a previously healthy child[27]. The assessment of quality of life has to be age-specific to address properly the health-related issues of each age and the burden related to a particular condition. The KIDSCREEN group is an international team of health professionals who had aimed to overcome the limitations of the international pediatric QoL instruments, by providing measures suitable for children, teenagers and parents and that can be used to both evaluate and monitor HRQoL in different settings[51]. The questionnaires were developed from a European cross-cultural widely representative health survey in countries all over the continent. They were both conceptually and linguistically validated in more than 30 languages. There are three versions of the KIDSCREEN questionnaires, as we explained previously. The longest versions cover specific dimensions of HRQoL (physical, mental and social well-being) while the short version represents a more global measurement. The KIDSCREEN questionnaire is simple and easy to use and it has become one of the preferred instruments to measure HRQoL in both public health and clinical medicine[61,62].

When applied to the surgical pediatric patient, items such as the relationship with their mates and the activities at school would be related with the return to normal activities after surgery and items regarding physical wellbeing could reflect issues regarding pain or scars. Therefore this kind of instruments could allow us to evaluate the results of a surgical intervention in terms of patient’s satisfaction, until more accurate and specific instruments could be developed.

However, as most of the HRQoL questionnaires specifically developed for children, it is not suitable to be used directly for a cost-utility analysis. The reason is because an instrument that could generate QALYs, has to have the potential to both "measure" and "value" health status by incorporating the individual preferences. Chen and cols developed a mathematical model to extrapolate the values of QALYs out of the results of the KIDSCREEN-10 questionnaire opening the door to the use of this simple and accurate instrument for cost-utility analysis in children[55].

The experience using this questionnaire during our study was very positive. Parents agreed to collaborate and it took only some minutes to respond to all the items. Thanks to the mathematical formula to extrapolate the results we found it both easy and suitable for an initial experience with this kind of studies for the surgical pediatric patient.

When analyzing the general results of each item of the questionnaire in both groups we found interesting that there were no significant differences in scores regarding general wellbeing, instead scores related to getting back to school and relationship with family and friends were better in LAp group. This results could mean that both groups felt equally regarding postoperative discomfort but in the LAp group there was not an influence on their daily activities with friends family and at school. Scores related to emotional wellbeing (feelings of sadness) however was apparently better in the OAp group.

We considered the possibility that the differences observed could be explained by the age of the patients instead of the surgical approach, because, as we stated before, there was a higher median age in the LAp group. We run a multivariate analysis to assess this issue and we confirmed that age was not related with the results in each item. In addition, the questionnaire version that we used was the one specifically designed for parents and caregivers, to avoid any difference we could have depending on patient's age and understanding of the questions.

On the whole, the final extrapolated QALYs value did not reflect these variations and although it was higher in the LAp group (0.77 vs. 0.75) this difference was not statistically significant.

As we can see in our results, the ICER for laparoscopic appendectomy was 18,122.73 euros/QALY, right under the threshold of 20,000 to 30,000 euros/QALY that we had established as the amount of money that we would pay for a quality life-year. This means that even though the expenses in the LAp group were significantly higher, they are justified, as they were associated with an increase in HRQoL and at the same time they remained under the λ threshold.

Moreover, we think that the increment in HRQoL could be even higher than we actually detected in our study, making the ICER even more cost-effective. The reason for this supposition is that the selection of patients on each group was not randomized, but based on surgeon's choice (along with availability of shared MIS equipment), which could probably lead to a higher number of younger and thin patients in the OAp group. It is common knowledge that OAp in these patients can be done by a small incision and postoperative pain and discomfort is probably less than in an open procedure in a teenager or obese patient. Therefore their scores in KIDSCREEN questionnaire might have been better. This could have finally made the incremental HRQoL smaller than it could really be.

We are convinced that pediatric MIS is the future of Pediatric Surgery, especially for long complex procedures that require larger incisions and have a more painful postoperative recovery. However to reach this point with advanced surgeries, we have to implement the use of MIS in both elective and routine procedures first, and reach standards of quality of care in all centers despite their volume of patients or their funding.

In the specific case of appendectomy, the laparoscopic approach has undeniable advantages in children, which we all have experienced. For instance, it facilitates the dissection in retrocecal, subserosal or atypical localizations of the appendix. Additionally, it avoids the blind dissection that sometimes is needed in an open procedure when the cecum is fixed and cannot be exteriorized. In the case of complicated appendectomy, it offers a clear view of all the fluid o collections allowing us a better cleansing and drainage of the peritoneal cavity. Finally, it is also extremely useful considering the possibilities of different differential diagnosis in children like congenital malformations or ovarian conditions in girls.

After some controversy at the beginning of its use, it has finally been stated a lower rate of complications such as abscess formation and wound infection after laparoscopic surgery[47].

For all these reasons, we consider LAp is probably the best first line therapy for pediatric appendectomy, although OAp should not be discouraged in highly selected patients. We have seen that the results in the KIDSCREEN questionnaire and the

QALYs were also good in the OAp group, only slightly under those of the LAp group, which means that in a specific subset of young and thin patients, with non-complicated appendicitis, OAp might still play a role.

Moreover, we could keep on working to improve the costs to try to reach an even more favorable ICER in many different ways.

Pediatric Surgeons could team up with the rest of surgical specialists with special interest in MIS to share the equipment and hardware. This could be particularly useful in low-volume Pediatric Surgery Centers. The reason is that when we share the most expensive MIS technology, the number of cases a year increases and the proportional total costs per patient decreases. We consider it is important to work in coordination with general surgeons, urologists and gynecologist for instance to try to have the best possible hardware and optimize its use and the costs by sharing it, compensating the initial costs, making technology available for all and improving the cost-effectiveness of our procedures.

Regarding the use of instruments, mechanical devices have failed to prove superiority over endo-loops for ligating the appendix in non-complicated appendicitis, and the latter are much cheaper[63]. Similarly, in favorable cases, dissection of the mesoappendix can be safely done by electrocautery, diminishing the costs considerably by avoiding the use of endo-sealer.

Obviously the surgeon has to have all the possible resources available in case of complex cases that require the use of more expensive technology and it is the surgeon choice to use the most suitable instrument for each case.

Regarding the single port appendectomy, there are studies that prove its cost-benefit, however some others question their real effectiveness, considering the overstretching of the umbilicus, with the consequent postoperative pain and concerns regarding the scars[45, 46].

Again, if we use the rationale of choosing the right patient for the right procedure we can save costs and increase the quality of life. Probably single port appendectomy is a perfect technique for a non-complicated appendicitis with a free appendix, not subserosal, not retrocecal, that can be easily delivered through the umbilicus without tension or excessive manipulation. Once inspected the abdominal cavity, if the appendix is not suitable for this approach, we could always continue to a traditional 3 ports appendectomy.

We would also like to highlight the importance of training. First of all, the more that we train the more confident we will be in our procedures, the lower the complication rates and the better the outcomes. Training should be a standard for both trainees and surgeons, especially in low volume centers where not many laparoscopic procedures are made per year[64]. We all know the difficulties of training on experimental models on animals, but there are artificial models and even low-cost simulators that are useful tools to make some exercises on a weekly basis[65]. By doing so, we will improve both our general results and the cost-effectiveness of our MIS procedures. Training will also help us to reduce operative times in MIS. In 2016, the FDA alerted about a potential negative effect on brain's development of certain anesthetic agents when used on patients under 3 years of age or over 3 hours or in repetitive times[66]. Although this is not the case of most pediatric appendectomies, there is an increasing concern about operative times. It seems logical to make an effort to try to reduce the time a child is under general anesthesia.

We have not measured the operative time in this study, but as we have explained previously, time has also a cost-opportunity. The extra time we spend doing a longer

MIS procedure is time we could be doing something else. Therefore, it is important to reduce the operative times, first of all for the patient safety, reducing time under general anesthesia, and secondly it will improve our cost-effectiveness as well.

Another point to take into consideration as well is the postoperative hospital stay after a laparoscopic procedure. Many studies in adult surgery state that this hospital stay is shorter than after an open procedure but in children it is not always that clear [9, 11]. In some centers there is a trend towards keeping a child at the hospital supervised after a MIS procedure with endotracheal intubation and even laparoscopic inguinal hernias are not done on a day-case basis. If the rational of MIS is shortening the hospital stay along with going back to normal routine activities as soon as possible, we should be able to dismiss the patient on the same operative day after a laparoscopic hernia repair or orchidopexy. There are even some authors that propose the laparoscopic appendectomy for non-complicated appendectomy as a day-case surgery[67, 68]. As the technique evolves and more experience is gained, we will be able to perform some procedures even without endotracheal intubation (ETI) and we will soon see this shortening in hospital stay[69].

On the whole, avoiding ETI along with shortening operative times and an earlier dismissal will diminish the "invasiveness" of the anesthetic component of the intervention leading us to the concept of global minimally invasive surgery in all different areas of the surgical procedure as a whole.

We would also like to highlight the capability of low volume Pediatric Surgery Centers such as ours to establish a proper pediatric MIS surgery program, based on experience, training, external stages to keep updated, good professional teamwork with adult surgeons and multi-institutional relationships to investigate and run clinical studies such as this one.

Our study has some limitations that we would like to discuss. First of all, its retrospective nature. There are not previous published papers considering HRQoL in pediatric MIS, therefore it is important to have some preliminary results regarding the feasibility of this kind of economical studies to set the basis for future research. This is the reason why we designed a retrospective pilot CUA to begin with. This retrospective design is the cause of another limitation of our data, which is the reduced number of patients included. We work in two low volume Pediatric Surgery Centers and we had to focus on non-complicated appendicitis and in patients older than 8 years old to be able to use the KIDSCREEN questionnaire. Additionally we could not go back in time too much to enlarge our sample because there could be a bias regarding the memories that the parents have about the postoperative period after a long time. However, the MCS allowed us to overcome this limitation by simulating different scenarios to help us to conclude de analysis have enough information to draw conclusions.

Our study would have been more accurate if the choice between OAp and LAp had been randomized. We analyzed the basal differences amongst the two groups in order to detect any possible influence on the results.

There are also some specific limitations of any CUA that we should keep in mind. The results of this kind of analysis are based on a model and data that is under conditions of uncertainty and under continuous evolution. It should be updated and tested any time new information or data is available on the field to make sure they are accurate.

Estimating costs is obviously one of the most difficult parts of these studies. We have gathered all the information related to prices, salaries and hardware directly from the providers, but there are many aspects whose costs are hard to determine. Non-medical and indirect expenses such as loss of productivity of the parents or caregivers have not been considered as they are very difficult to assess and they can vary in each family, for instance depending on if they have someone to take care of the child at home.

On the whole, direct costs alone underestimate the real cost and burden of a disease or a surgical procedure as in our case, but in spite of it, they give us an approximate idea of the differences in costs between two interventions.

The accuracy of our measurements of HRQoL is even better when we have a basal measure to which compare the postoperative one, something that we will take into consideration for future research in elective pediatric MIS procedures.

On the whole, we consider the results of our study to be worth to take into consideration in spite of its limitations. They could be the basis of future research, prospective and randomized, in which we could evaluate the HRQoL from the very precise moment of the indication in any pediatric MIS procedure and during the postoperative period.

Gathering information regarding costs and HRQoL in future studies may provide us with further insight into the economic and social perspective of pediatric MIS and its final outcomes in terms of children's quality of life.

CONCLUSIONS

- Cost-utility analysis allows us to prove the suitability of pediatrics MIS procedures in terms of health-related quality of life and its results may justify the use of this approach in Pediatric Surgery.
- LAp is cost-effective against OAp for non-complicated appendectomy in children.
- An effort should be made on developing specific tools that could allow us to assess QoL in the pediatric surgical patient.
- Future research should be undertaken in different indications and settings to guide an evidence-based approach to pediatric MIS in a QoL-based healthcare economy.

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