

Early post-operative interleukin-6 and tumor necrosis factor- α levels after single-port laparoscopic varicocelectomy in children

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Abstract

Purpose Laparoendoscopic single-site surgery has recently been described in children and regarded as an improved technology leading to less pain and better cosmetic outcome. Compared to the traditional three-port method, it is not known if the single-port method is less invasive. The aim of this study was thus to investigate the post-operative acute inflammatory response in order to evaluate surgical stress in the two surgical approaches in children.

Methods A prospective, single blinded, case-control study was carried out. Thirteen male patients who presented with unilateral varicocele were divided into two groups. Six children underwent single-port laparoscopic procedure, while the other seven children underwent three-port laparoscopic procedure. Pre-operative and post-operative blood samples were taken for the measurement of tumor necrosis factor- α (TNF- α) and interleukin 6 (IL-6) using ELISA. Demographics including the operation time, and complications were recorded. Data between the two groups were analyzed using unpaired *t*-test and a *p* value of <0.05 was taken as statistically significant.

Results The mean age of patients was 14.5 years (range 12–19 years). There was no significant difference between the two groups in terms of operative time, nor there was any complication recorded. The change in serum TNF- α and IL-6 concentrations pre- and post-operatively between the single-port group and three-port group was not statistically significant. Overall, patients in the two groups showed excellent satisfaction in terms of post-operative cosmesis.

Conclusion Single-port laparoscopic varicocelectomy is safe, effective and produces excellent cosmesis with minimal surgical stress.

Keywords Single-port laparoscopy · Varicocele · Surgical stress · Interleukin-6 · Tumor necrosis factor- α

Introduction

Laparoscopic surgery is now a well-accepted alternative and in some cases, is even the preferred treatment modality to open surgery for many conditions. In this regard, the benefits of laparoscopy on postoperative pain, wound cosmesis, hospital stay, and convalescence are widely recognized. Nonetheless, surgeons across the world still strive to improve on existing techniques to try to improve the outcomes of these parameters. Recently, further advances in laparoscopic surgery have resulted in significant innovations, with the emergence of natural orifice transluminal endoscopic surgery (NOTES) and single-port access surgery.

Single-port access surgery, embryonic natural orifice transumbilical endoscopic surgery (E-NOTES) or laparoendoscopic single-site surgery (LESS), which utilizes access via the umbilicus, has received increasing popularity

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recently. With this technique, the surgical scar is virtually concealed within the umbilicus, an embryonic natural orifice [1–3]. Furthermore, there is no concern like those seen in NOTES procedures. The technique was firstly described by Pelosi and Navarra [4, 5] for single-puncture laparoscopic appendectomy and cholecystectomy. Since then, references for LESS have been well reported in adults and children [1, 6–8]. Due to the hidden intra-abdominal entry point in the umbilicus, the feature of “scarless” has made it as a rapidly evolving field.

Despite worldwide enthusiasm, only scarce data are available comparing traditional three-port method with the single-port method in terms of post-operative stress. Although post-operative stress typically encompasses a wide range of endocrinologic, immunologic and hematologic effects, the markers of inflammation are mostly secondary to tissue injury from the minimally invasive procedures. Initial inflammatory response, stimulated by tissue trauma or sepsis, is characterized by the production of pro-inflammatory cytokines, in which interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α) are regarded as influential and widely investigated in inflammation research [9]. Surgery provokes an early increase in circulating levels of IL-6 within 1–3 h [10]. The level will remain elevated for 2–3 days postoperatively [1, 7]. On the other hand, an increase in TNF- α level is seen in patients with post-operative sepsis [11]. Thus, the increase in IL-6 but not TNF- α may reflect post-operative stress due to tissue trauma alone, which in turn, is dependent on operative time, blood loss, and the extent of tissue trauma [6]. We may thus argue that higher levels of IL-6 from the single-port method is expected since it involves a 2.5 cm incision versus three 5 mm incisions totaling only 1.5 cm. The primary aim of this study was to investigate early post-operative stress response in order to evaluate surgical stress in children who underwent single-port and three-port laparoscopic varicocelectomy. Secondary outcomes also included clinical parameters and post-operative wound cosmesis.

Methods

A single-blinded, prospective case-control study was carried out between September 2009 and March 2010 on 14 boys (mean age = 14.5 years, range 12–19 years) who presented with unilateral varicoceles. The children who underwent surgery all had grade III varicoceles. Six children underwent single-port laparoscopic procedures while the other seven children received traditional three-port laparoscopic procedures. All subjects had no sign of inflammatory disease before surgery. Operations were

performed under general anesthesia and carried out by two specialist surgeons for this study. Informed consent was obtained from each patient according to the protocol of the Ethics Committee of the Queen Mary Hospital of the University of Hong Kong.

Operative techniques

For the single-port laparoscopic technique, a 2.5 cm transumbilical incision was made down to the peritoneal cavity. Under direct vision, Triport™ (Olympus Inc., USA), a specially designed single port with three inserts, was placed into the peritoneal cavity and secured. A 5 mm laparoscope was used for visualization and two 5 mm straight working instruments were inserted. The testicular vessels were clipped en mass and divided. For the traditional three-port method, a 5 mm camera port was inserted transumbilically. Two further 5 mm working ports were inserted in the right and left flanks, respectively.

Blood collection and ELISA assay

Blood samples were taken before surgery and 1 h after surgery by the same nurse. Blood samples were allowed to clot for 30 min, and then centrifuged for 15 min at 1000 \times g (4°C). Serum was aliquoted and stored at –80°C until testing. The samples were thawed once and assays were conducted in triplicate. Serum IL-6 and TNF- α levels (pg/ml) were determined by quantitative sandwich enzyme immunoassay using Human High Sensitivity ELISA kits (R & D Systems, Minnesota, USA). The manufacturer’s instructions were followed for testing. Reported sensitivity thresholds in plasma to be 0.5 and 0.156 pg/ml for TNF- α and IL-6, respectively. All laboratory tests were conducted by the same staff who was blinded to the clinical status of the individual subjects.

Clinical variables

Medical history and demographic data were collected prospectively including operative time, blood loss, post-operative complications, analgesic requirements and hospital stay. Post-operative pain was measured 2 and 4 h post-operation and just prior to discharge, using the visual analog (VAS) (Fig. 1) [12]. If the score was ≥ 4 , the patients were given paracetamol at 15 mg/kg/dose.

Patient satisfaction on post-operative scar appearance was surveyed at outpatient visit 3 months after the surgery. Cosmetic result was scored by patients using the following scale: unsatisfactory = 0, satisfactory = 1, good = 2, and excellent = 3.

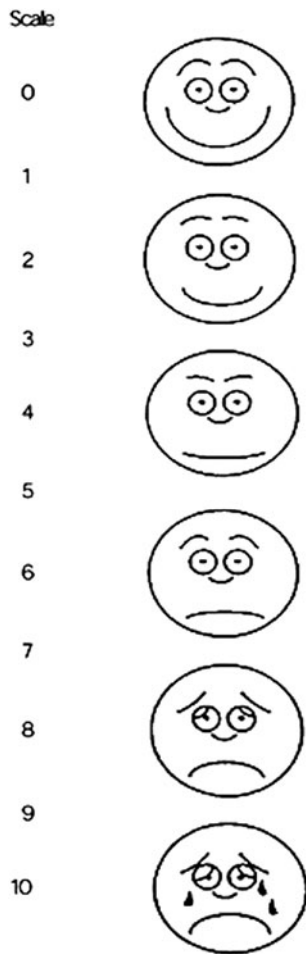


Fig. 1 The use of visual analog scale for assessment of post-operative pain

Statistical analysis

Unpaired *t*-test with mean and standard deviations was used for comparisons of percentages and means for normally distributed data and a *p* value of <0.05 was considered to be significant.

Results

The average age in single-port group was 15.3 ± 2.6 years and 13.7 ± 1.6 years in three-port group. All procedures were completed successfully by using either the single-port or three-port technique. There was no significant difference between the two groups in terms of operative time, post-operative complications recorded, and analgesic usage (Table 1). Every umbilical incision was hidden nicely within the umbilicus. At a mean follow-up of 7.8 (range 6–10) weeks, there was excellent cosmetic result, even with a larger 2.5 cm incision in the single-port group

Table 1 Demographic, peri-operative and post-operative data of patients

| | Single-port group (<i>n</i> = 6) | Three-port group (<i>n</i> = 7) | <i>p</i> value |
|-------------------------------|--------------------------------------|-------------------------------------|----------------|
| Age at operation (years) | 15.3 ± 2.6 | 13.7 ± 1.6 | >0.05 |
| Operative time (minutes) | 38.5 ± 6.9 | 33.3 ± 13 | >0.05 |
| Blood loss (mls) | 0 | 0 | >0.05 |
| Doses of paracetamol required | 0.71 ± 0.18 | 0.57 ± 0.2 | >0.05 |
| Hospital stay (days) | 0.33 ± 0.52 | 0.43 ± 0.53 | >0.05 |

(Fig. 2), with no recurrence or surgical complications as hydrocele, infection, or incisional hernia.

Changes in inflammatory cytokine profiles

The change of TNF- α concentration in serum was 0.324 ± 0.406 pg/ml between pre- and post-operatively in the single-port group (*n* = 6), while in the three-port group (*n* = 7), the change of its level was 0.329 ± 0.952 pg/ml (*p* = ns). There was no significant difference in the change between groups (Fig. 3a).

The change of IL-6 in serum concentration was 0.151 ± 0.392 pg/ml between pre- and post-operatively in the single-port group, and in the three-port group, the change of its level was 0.097 ± 0.929 pg/ml (*p* = ns). No significant difference could be seen in the change between groups (Fig. 3b).

Cosmesis and patient satisfaction

Patients' satisfaction on the cosmesis was not significantly different, although there seemed to be a trend towards better satisfaction in the single-port group (Table 2).

At 3 months postoperatively, the mean cosmetic score was 2.71 for the single-port group and 2.57 for the three-port group.

Discussion

Laparoendoscopic single-site surgery (LESS) marked the beginning of a new era in the field of modern minimally invasive surgery. Refinement and modification of laparoscopic instrumentation has resulted in a substantial increase in the use of LESS over the past 4 years. Several centers have already demonstrated the feasibility and safety of LESS in patients with urologic disorders [13–16]. In LESS pediatric procedures, decreased post-operative pain, improved cosmesis and faster recovery have been reported [8]. Traditional laparoscopic operation requires three to six ports. Each port increases the potential risk of bleeding,



Fig. 2 A post-operative photograph of the umbilical wound taken 1 month after single-port varicocelectomy

port-site hernia, internal organ damage, and decreases cosmetic outcome [17–19]. Single-port laparoscopic surgery could greatly reduce the aforementioned problems of laparoscopic surgery. Indeed, many recent reports in adults have been published to show the advantages of single-port procedures over the traditional three-port approach [1, 14–16, 20–24]. However, compared to the traditional three-port method in children, the exact advantages for single-port method are sparse.

Surgical stress is characterized by an induced production of pro-inflammatory cytokines [25, 26], TNF- α and IL-6 are two well-known pro-inflammatory cytokines which are thought to be central mediators in the cytokine cascades, and also important cytokines for immune and inflammatory response. The changes in serum TNF- α and IL-6 concentration are sensitive indicators of the post-operative acute phase inflammatory reaction and surgical stress [27–29]. However, only a rise in IL-6, but not TNF- α is seen in stress due to tissue trauma. Thus, in our preliminary study, these two cytokines were used to evaluate and differentiate surgical stress and injury between single-port and three-port laparoscopic varicocelectomy in children. LESS pediatric procedure needs one bigger incision to be passed through by three trocars. A lack of triangulation among right, left instruments and the laparoscope makes procedure more difficult to perform. Furthermore, external instruments may clash inside the peritoneal cavity. In addition, the operation time will be longer for surgeons who lack adequate experience. These negative factors may result in an increase in the level of inflammatory response. In our study, results showed that there were no significant differences between

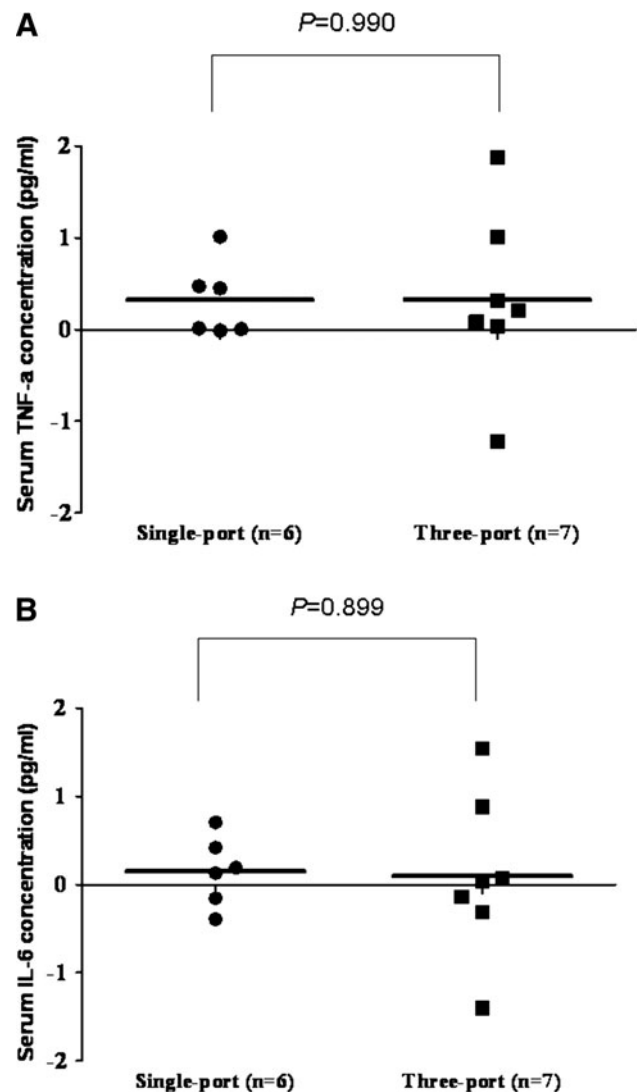


Fig. 3 Dot plot indicates the change of TNF- α (a) and IL-6 (b) concentration in serum between pre- and post-operatively in two groups. The horizontal line in dot clusters of each individual group indicates the mean values in the corresponding groups. Unpaired *t*-test was used for comparison between 2 groups

Table 2 Post-operative cosmetic scores after 3 months

| Single-port group (n = 6) | Three-port group (n = 7) | <i>p</i> value |
|------------------------------|-----------------------------|-----------------|
| 2.71 | 2.57 | <i>p</i> > 0.05 |

the two groups in terms of clinical data. We believe that with the improvement of laparoscopic instruments, and the accumulation of experience, the advantages of LESS surgery in the pediatric population will become more apparent. Nonetheless, there are some important limitations of the current study. First, our findings were limited by the small number of patients included. Second, the disease category

chosen was relatively minor and thus the overall post-operative inflammatory response would be low, no matter what technique was used. These should be overcome in a future larger study on a different disease condition.

Laparoendoscopic single-site surgery probably represents the next evolutionary step in laparoscopic surgery. However, as we are only at the beginning of a new minimally invasive technology, some questions surrounding the use of LESS still remain unanswered. Firstly, the technical challenges of performing LESS due to minimal or no triangulation of the instruments has to be overcome, and this is limited by the equipment available, at least in the pediatric population. Furthermore, several related clinical questions must be considered. For example, what is the best way to extract large specimens? In addition, patients' attitudes about scar-free surgery have only been evaluated by a simple questionnaire. The differences of cost between single- and three-port laparoscopy are also not known.

In conclusion, we showed in our preliminary study that LESS produced similar stress response to traditional laparoscopy. Further clinical investigations and longer follow-up period are necessary to elucidate the true benefit and utility of this novel surgical approach compared to current alternatives.

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