Abdominal wall hernia repair : intraperitoneal mesh and adhesions

VALORISATION

Knowledge valorisation is the process of creating value from knowledge, by making knowledge suitable and/or available for economic and/or social use and by translating knowledge into competitive products, services, processes and new commercial activities[1]. A perspective on the valorisation of the work presented in this thesis follows here.

Relevance

Spontaneous hernias (e.g. epigastric, umbilical, inguinal) and iatrogenic hernias (e.g. incisional, parastomal) of the abdominal wall still are two of the most frequently encountered problems in surgery. In fact, one in four men develops an inguinal hernia at some point in his life resulting in inguinal hernia repair being the most frequently performed operation worldwide (estimated 20 million hernias repaired every year)[2]. The rest of the abdominal wall hernias occur less frequently, though over 1.8 million patients with an abdominal wall hernia are operated per year in the USA and numbers seem to be increasing[3].

Most abdominal wall hernia repairs are regarded as minor surgery with low associated risks. Nevertheless, the high number of operations, combined with the significant risks of developing a recurrence or chronic pain, make hernia repair an intervention that has a significant influence on overall surgical morbidity and health expenditure[2,3].

Postoperative adhesion formation is probably the most common long-term complication from abdominal surgery that may cause female infertility, bowel obstruction, pain and bowel injury at reoperation. The impact of adhesions on national health expenditure is estimated at more than 2 billion dollars per year in the USA[4].

Foreign bodies implanted intraperitoneally, such as meshes for hernia repair, are a specific lead point for adhesion formation or even worse, fistula formation[5]. As a result, complications from intraperitoneal mesh placement could be significant and are worth preventing from an individual patient's as well as a societal point of view.

Target groups

The results of this thesis are of interest to a wide audience. Firstly, all medical professionals and surgical specialists in particular, should appreciate adhesions as a possible, or even likely cause of female infertility, bowel obstruction or bowel injury at reoperation with patients that underwent abdominal surgery in the past. In addition, surgical specialists should try to prevent adhesion formation and inform patients preoperatively at all times. General practitioners also have a role in recognizing patients with a history of abdominal surgery to be at risk for adhesion related complications.

With regards to the use of antiadhesive agents, the direct costs associated with these products are probably an important impediment for their widespread use[6]. Nevertheless, routine use of such products among high risk patients is very likely to prove cost effective[7]. As such, health insurance companies and reimbursement agencies should consider providing adequate funding for the use of antiadhesive agents.

With regard to the antiadhesive effects of mesh coatings, it is important to note that most of the different coatings do not show significantly different results in an experimental setting. Also in terms of other variables such as mesh incorporation, results seem to be very similar. This implies that, in the absence of sound clinical evidence, policy makers (either hospital or national) should be able to base their choice for certain mesh products also on other parameters such as costs and mesh handling.

Lastly, patients should also be encouraged to inform themselves about the operation related risks of adhesions and their prevention. An active role from these patients, preferably in the form of a patients' association, will encourage both treating surgeons and policy makers to change current practice.

Activities and products

The results on adhesion awareness showed a significant underestimation of the clinical problem of adhesions and related morbidity by general surgeons[6]. In response, a similar survey was undertaken for Dutch gynaecologists[8] and general practitioners. Furthermore, the Dutch Adhesion Group was created by general surgeons and gynaecologists with a primary aim to raise awareness on abdominal adhesions. Today, reviews on the burden of adhesions and antiadhesive agents have been performed and published in outstanding clinical journals[4,9]. Hopefully, these publications have increased the awareness on adhesions and changed clinical practice. At this moment new surveys on adhesions are being prepared to measure these anticipated effects with the earlier studies serving as a benchmark.

As for the findings on cromolyn treatment significantly reducing postoperative adhesions, a patent has been filed for the application of cromolyn in adhesion reduction (publication number EP2638904A1, application number EP20120159348). Although cromolyn is already a long known drug in the prevention of asthmatic attacks, it was pushed aside in favour of steroids and beta 2 adrenergic agonists. Today, the indications for use seem to expand and a supposed suppression of the innate immune system helps to limit intraperitoneal adhesion formation.

Lastly, our pilot study on parastomal meshes showed that it is probably safe to place prosthetic meshes at the time of stoma creation in order to prevent incisional hernias after stoma reversal.

Innovation

In this thesis several innovative aspects in terms of valorisation have been addressed. Two of the most important innovations include the administration of cromolyn to reduce adhesions and the application of a parastomal mesh in temporary stoma formation to prevent incisional herniation after stoma reversal.

Firstly, until now, adhesion prevention in intraperitoneal mesh placement had been mainly achieved through addition of coatings that locally shield the abdominal wall and mesh from intraperitoneal contents. Despite different substances used for these coatings, no further improvements in terms of adhesion reduction seem to be obtained. Therefore, we

decided to approach the problem from another angle. We showed that preparing the host optimally for implantation of the mesh could attain adhesion formation. What is more, the required treatment is limited to three pills, one pill per day, taken from 2 days until 4 hours before the operation. All in all, this simple treatment with pills administered preoperatively would be easily applicable and seems to be free from evident side effects.

Secondly, recent trials have shown that prophylactic parastomal mesh placement almost fully eliminates the high rates of parastomal hernias[10]. However, these findings are limited to definite stomas. Nevertheless, in temporary stoma formation about one in three stomas eventually turn out to be a definite stoma as well. Furthermore, we showed that the patients that have a stoma reversed are at a very high risk for incisional herniation at the site of the old stoma wound. Therefore, we conducted an interventional study on prophylactic mesh placement at the time of temporary stoma formation. The two-year follow-up results showed no signs of infection or incisional hernias. Combining our results with the findings in temporary stomas suggests that every stoma, both definite and temporary, should be reinforced with a parastomal mesh at the time of construction.

Schedule and implementation

Several interesting opportunities follow from the research described in this thesis.

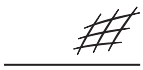
As for the application of cromolyn in a clinical setting, only limited additional experimental testing in an oncological and anastomotic experimental model would be required before commencing a clinical trial. Moreover, oral cromolyn is currently already registered in the USA, and in much higher doses than the doses that can be calculated from our experimental studies. No apparent side effects, apart from allergies to the drug have been noticed. In Europe, oral cromolyn used to be registered but was pushed away by other drugs. Importantly, production costs of cromolyn are very low, comparable to acetaminophen (paracetamol). Because of the above, it seems that a phase II study can be initiated without too many hurdles. In such trial, the most important challenge will be to determine a suitable outcome parameter. Because of the long follow-up required for adequate observation of bowel obstruction, infertility rate and bowel injury at the time of reoperation, surrogate outcome parameters should be used. One such parameter could be the extent and type of adhesions as examined in our model of prophylactic parastomal mesh placement[11].

Another important finding is the successful application of a parastomal mesh in temporary stomas. Together with the fact that these meshes have a role in definite stomas, and even in an infected milieu[12], the application of a parastomal mesh should be a standard of care in constructing any type of stoma. A large scaled trial should confirm possible benefits in terms of quality of life and cost effectiveness.

It seems logical that for both proposed studies, the respective manufacturers of cromolyn and meshes will be engaged. In addition, governmental support should be aimed for as well, e.g. for cost effectiveness research. Important for both studies is the fact that in case of positive results high numbers of patients will be treated accordingly in the future which should help to make the case for cromolyn and mesh manufacturers. However, also because

of the high number of affected patients, even small improvements in quality of life or cost effectiveness per patient can have major impact on societal health care (management).

Lastly, the mesh specimens taken from our human trial with parastomal mesh should be compared against the specimens from our experimental studies. If no significant correlation between the clinical and experimental setting exists, future experimental research should be further scrutinized. Until now, no such data are available in the literature.



References

1 Interdepartementale Programmadirectie Kennis en Innovatie, Innovatieplatvorm. Van voornemens naar voorsprong: Kennis moet circuleren. Den Haag: 2009.

2 Kingsnorth A, LeBlanc K. Hernias: inguinal and incisional. *Lancet* 2003;362(9395):1561–71.

3 Poulose BK, Shelton J, Phillips S, Moore D, Nealon W, Penson D, Beck W, Holzman MD. Epidemiology and cost of ventral hernia repair: making the case for hernia research. *Hernia* 2012;16(2):179–83.

4 Broek ten RPG, Stommel MWJ, Strik C, van Laarhoven CJHM, Keus F, van Goor H. Benefits and harms of adhesion barriers for abdominal surgery: a systematic review and meta-analysis. *Lancet* 2014;383(9911):48–59.

5 Halm JA, de Wall LL, Steyerberg EW, Jeekel J, Lange JF. Intraperitoneal polypropylene mesh hernia repair complicates subsequent abdominal surgery. *World J Surg* 2007;31(2):423–9.

6 Schreinemacher MHF, Broek ten RP, Bakkum EA, van Goor H, Bouvy ND. Adhesion awareness: a national survey of surgeons. *World J Surg* 2010;34(12):2805–12.

7 Wilson MS, Menzies D, Knight AD, Crowe AM. Demonstrating the clinical and cost effectiveness of adhesion reduction strategies. *Colorectal Disease* 2002;4(5):355–60.

8 Meuleman T, Schreinemacher MHF, van Goor H, Bakkum EA, Dörr PJ. Adhesion awareness: a nationwide survey of gynaecologists. *Eur J Obstet Gynecol Reprod Biol* 2013;169(2):353–9.

9 Broek ten RPG, Issa Y, van Santbrink EJP, Bouvy ND, Kruitwagen RFPM, Jeekel J, Bakkum EA, Rovers MM, van Goor H. Burden of adhesions in abdominal and pelvic surgery: systematic review and met-analysis. *BMJ* 2013;347:f5588.

10 Timmermans L, de Goede B, Eker HH, van Kempen BJH, Jeekel J, Lange JF. Meta-analysis of primary mesh augmentation as prophylactic measure to prevent incisional hernia. *Dig Surg* 2013;30(4-6):401–9.

11 van Barneveld KWY, Vogels RRM, Beets GL, Breukink SO, Greve J-WM, Bouvy ND, Schreinemacher MHF. Prophylactic intraperitoneal mesh placement to prevent incisional hernia after stoma reversal: a feasibility study. *Surg Endosc* 2014;28(5):1522–7.

12 Argudo N, Pereira JA, Sancho JJ, Membrilla E, Pons MJ, Grande L. Prophylactic synthetic mesh can be safely used to close emergency laparotomies, even in peritonitis. *Surgery* 2014;156(5):1238–44.