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European Association of Urology



Letter to the Editor

Synthetic Vaginal Tapes for Stress Incontinence: Proposals for Improved Regulation of New Devices in Europe

1. Introduction

The regulations governing the introduction of new drugs and new medical devices are very different, with a widespread view that devices should be scrutinised more carefully than is currently the situation before being introduced into clinical practice. The timing of this paper is very appropriate given the series of papers published by the *British Medical Journal* in May 2011 [1]. These papers centred on concerns about the regulations of devices with respect to a certain metal used in metal hip replacements.

In the field of stress urinary incontinence (SUI), a number of new devices including synthetic vaginal tapes have become widely used in the last decade. This paper results from a workshop held at the Medicines and Healthcare Products Regulatory Agency (MHRA) in March 2011 and arose through concerns from the MHRA with respect to the number of adverse events reported following insertion of synthetic tapes for female SUI. The MHRA, the UK government organisation responsible for the regulation of medical devices, contacted urologists and gynaecologists active in this field and also invited some of the relevant manufacturers to attend a day-long meeting.

The MHRA has received an increasing number of reports of adverse events resulting from the use of tapes for SUI from manufacturers, users, and the public, with 42 reports in 2010. The total number of tapes implanted in 2010 is unknown, and therefore the denominator is not clear. However, there is also an underlying concern at MHRA of a marked underreporting of the complications from these devices.

This paper reports on the issues discussed at the meeting under the headings of product development, clinical adoption, clinician training, the reporting of outcomes and adverse events, and finally, it lists the proposed responsibilities for manufacturers, the regulator, and clinicians.

2. Product development

The term *tapes* used in this paper means the material is synthetic. The term *sling* is used when the material is

biologic and in the case of SUI when the sling is made from biologic material (eg, from autologous material such as rectus sheath or fascia lata).

Synthetic tapes have now been used for almost 15 yr, and there has been an evolution in the materials used. All currently available synthetic slings are made from monofilament and macroporous polypropylene. Hence new developments have focused on the introduction of coloured tapes, heating part of the tape to reduce shrinkage, the route of deployment of the sling, and most recently the length of the sling.

When a manufacturer produces a new device, it can either be regarded as evolutionary or revolutionary, with most new devices probably regarded as the former. The meeting attendees felt this was largely a semantic argument and not particularly useful. Their view was that all new devices should undergo appropriate clinical trials to establish individual safety and performance for the purpose of Conformité européenne (CE) marking and in the postmarket phase undergo comparative studies to assess the real difference(s) between the new tape and the existing available tapes.

Under current legislation, before marketing any new device the manufacturer must decide whether its product is a medical device and if so how it is to be classified (I, IIa, IIb, or III). Tapes are class IIb devices; devices such as a heart valve are class III.

The manufacturers then make a case to a Notified Body (NB) for the device to be assigned a CE mark. The NB is an organisation accredited by the Competent Authority that is responsible, along with the manufacturer, for deciding whether the body of evidence on the safety and performance of the device is sufficient to demonstrate compliance with the essential requirements and thus allowing the affixing of a CE mark. To demonstrate that the device complies with the essential requirements, the manufacturer must generate clinical data. These data can be generated either from the results of a specifically designed trial or from results generated from studies of similar devices where equivalence can be demonstrated.

The clinicians at the meeting felt that the decision, with regard to the required clinical data, was potentially the weak part of the process and in direct contrast with the system involved in the licensing of new drugs. Even if a new drug is similar to existing drugs in the same class, it still requires full testing.

3. Introducing a new device into clinical practice

All UK hospitals have a committee that looks at new procedures and devices that will be used for the first time in that National Health Service hospital. If a surgeon wishes to use a new device, he or she is expected to bring this device before that relevant trust committee. If the device is not an accepted treatment, and if it has not been looked at by the National Institute of Health and Clinical Excellence (NICE) Interventional Procedures Advisory Committee (IPAC), then the trust expects the surgeon to notify NICE of the procedure and request that NICE/IPAC produce guidance for the new device.

The manufacturers presented a synopsis of their training policies for surgeons who had not previously used their device. A range of training methods were used that included cadaver training, the surgeons visiting an established user of the device, and the surgeon being mentored by experienced surgeons in his or her own hospital. The clinicians at the meeting felt that the practice described was a good standard, although the surgeon had no obligation to accept the offer of training/mentorship. To address this point, the meeting attendees felt that the relevant trust committee that looked at new devices and procedures should insist that the surgeon undergo proper training and mentorship before using the device independently. It was suggested that it would be useful for the British Association of Urological Surgeons' (BAUS) Section of Female, Neurological, and Urodynamic Urology (SFNUU) and the British Society for Uro-Gynaecology (BSUG) to produce a standard for training/mentorship for those surgeons wishing to implant a tape that was new to their practice.

Manufacturers produce an instruction manual for new devices. However it was expressed that such manuals were not regularly updated with new procedural developments attained in the postmarket phase by surgeons when using a new device. Many at the meeting felt that a formal review and update of the training manual should be carried out every 6 mo after the introduction of a new device as a result of new information (eg, feedback from implanting surgeons to the manufacturer).

4. Device implantation in a safe environment

4.1. Patient selection

The NICE guidelines for incontinence describe a number of steps in management:

- Women with the symptoms of SUI should initially be offered lifestyle interventions such as weight loss and pelvic floor muscle exercises, including teaching of the “knack.”
- If conservative measures fail, and the woman wants to consider surgery for her SUI, urodynamics are recommended unless she has “symptoms of pure SUI.” Recent work has shown that only 5% of women fit into that category, however, and 25% of those have other important urodynamic abnormalities [2]. The specialist professional

organisations recommend urodynamics before any invasive procedures for SUI, to predict any postoperative problems and maximise good outcomes, as well as for all women with mixed urinary incontinence (stress plus urgency incontinence).

5. Reporting of patient outcome and adverse events

At present there is no obligation to follow up patients after surgery or to assess outcome. Postmarketing registries have been started by professional bodies, for example in the United Kingdom by the BAUS SFNUU and BSUG. In addition, some manufacturers have also started registries for tapes used in treating SUI.

Outcomes could be determined by tracking patients who received a new tape, which would be facilitated if a unique sticker was provided with each tape, attached to the patient's operation note, and a simple questionnaire was produced with each tape for completion by the surgeon at the time of the operation. This could be used to establish a register of the procedure. An implant card might also prove useful.

These methods would allow each tape to be tracked and for patient outcome and any adverse events to be reported, although, as pointed out earlier, at present, there is no obligation to follow patients or to use registries. However, it is likely that the General Medical Council will introduce a system of enhanced appraisal that will be used as the basis for the 5-yr revalidation of surgeons. In an enhanced appraisal it is likely to become mandatory for surgeons to enter all their patients in databases and to formally assess outcome.

6. Reporting of adverse events

All adverse events should be reported to both the MRHA and the manufacturers. The MHRA has a process for accepting reports of adverse events from manufacturers, users, and patients. This facility can be accessed via the MHRA Web site, www.mhra.gsi.gov.uk. However, the MHRA believes there is significant underreporting of adverse events, and the clinicians present said they believed this to be the case and thought a “red card” or a similar system for reporting device-adverse events should be introduced. This would be similar to the well-recognised and better used “yellow card” system for reporting drug-adverse events.

It was felt that the BAUS SFNUU and the BSUG should produce a list of adverse events that could be part of an outcome assessment. This could include the following adverse events:

- Bleeding/haematoma
- Urinary retention/voiding dysfunction, including the need for an indwelling catheter or intermittent catheterisation
- Sling malpositioning, or erosion, to vagina, bladder, suprapubic skin and thigh
- Sepsis in the form of urinary infections, suprapubic infections, or skin infections

- Pain in the suprapubic, vaginal, or thigh areas
- SUI incontinence, either persistent or recurrent
- Urgency incontinence either persistent or de novo
- Need for reoperation due to bleeding, need to loosen the tape, or cut the tape, and to treat persistent or recurrent SUI.

7. Future research

The need for randomised controlled trials (RCTs) at an early stage of development of any new device, with significant new features compared with existing tapes, was felt to be essential. The clinicians expressed regret about the number of low-quality studies, usually case series, published in the literature. It was felt that it will be useful to encourage editors of urology and gynaecology journals to reject such papers in favour of only publishing RCTs and other high-quality research. This would send a message to clinicians that they need to invite their patients to take part in high-quality RCTs to establish at an early stage whether a new device is safe and effective and an improvement on the existing synthetic tapes for SUI.

8. Responsibilities of the involved parties

Three main groups of involved parties were discussed: the manufacturers, the regulatory authorities (the MHRA in the UK), and the surgeons, both urologists and gynaecologists.

8.1. Manufacturers

Manufacturers' responsibilities should include the following tasks:

- Testing the device thoroughly, including carrying out appropriate clinical trials, before placing on the market.
- Ensuring that clinical data are appropriate (ie, the equivalence route for obtaining clinical data is relevant to the product in question).
- Ensuring that "Instructions for Use" are comprehensive, regularly updated, and user friendly and that any changes are communicated with relevant clinicians.
- Ensuring that there are sticky labels in the "Instructions for Use" that identify the individual tape, for attachment in the patient's case notes.
- Ensuring that there are adequate training programmes.
- Ensuring that appropriate postmarket surveillance programmes are in place, including postmarketing registers designed to collect appropriate numbers of patients treated, with adequate duration of follow-up, and appropriate end points including long-term safety and efficacy.
- Ensuring that appropriate action is taken as indicated by the results of the postmarket surveillance programme, especially in terms of updating criteria for use, special precautions, etc.
- Reporting all serious adverse events to the competent authority (MHRA in the United Kingdom), ensuring

appropriate and timely investigation, instituting suitable actions, and communication with users and manufacturers.

8.2. Medicines and Healthcare Products Regulatory Agency (Regulator/Competent Authority)

The regulator has the following responsibilities:

- Investigate all adverse events reported to MHRA with the manufacturer if appropriate. Ensure discussion with experts when required and ensure all identified actions are taken.
- If issuing a Medical Device Alert, ensure adequate discussion takes place with both manufacturers and clinicians so that relevant clinical advice is developed.
- Promote a specific professional Web page for urologists on the MHRA Web site (similar to those available for other professional groups).
- Encourage the use of the MHRA online reporting system by clinicians for all device-related adverse events (need strategies to address this).
- Ensure feedback to clinicians, by means of Royal Colleges/Professional Bodies, about adverse events and their outcomes at regular time intervals.

8.3. Clinicians dealing with female stress incontinence

Clinicians and their professional organisations should:

- Choose devices that have adequate clinical data to support their safety and efficacy. If a new device is being introduced, ensure endorsement by the relevant hospital committee. Choose a device for purchase and use from a company that offers an adequate training programme.
- Ensure familiarity with NICE Appraisal, Guidelines, and NICE Interventional Procedures Advisory Committee guidance prior to use.
- Ensure they have had adequate training.
- Ensure that all participating clinicians take part in refresher courses, if necessary, to update technique and review any updated changes in the Instructions for Use.
- Ensure proper patient selection: in the United Kingdom according to the NICE guidelines 2006 (to be updated in 2013).
- Ensure explicit patient information and consent, with full discussion with the patient on alternative treatments and side effects including pain and obturator nerve injury in addition to the more routine complications such as bladder perforation and haematoma.
- Ensure that details of the implanted device are entered into the patient's case notes: manufacturer, model, batch number, and device unique identifier.
- Ensure that BSUG and BAUS SFNUU prepare a list of adverse events that could be part of an outcome assessment.
- Report all adverse events to MHRA and to the manufacturers (www.mhra.gov.uk/safetyinformation/reportingsafetyproblems).

9. Discussion

Clinicians have long held the view that devices should not be introduced until there is clear evidence of their safety and efficacy when compared with existing means of treating SUI. In at least two instances, devices were withdrawn because of an unacceptably high level of adverse events. From the perspective of the manufacturers, it is in their commercial interest to bring their product to market as early as possible in its life span. Increased regulations and a marked increase in the demand for clinical data could possibly prejudice the commercial viability of an individual device. Clinicians are well aware of this problem, but this does not negate the need for proper evidence before the introduction of any new and significantly different product.

The amount of evidence needed before a device is marketed will vary, depending on the data needed to demonstrate compliance to the Medical Device Directive Essential Requirements for each device. These proposals introduced the concept of evolutionary or revolutionary design. Perhaps the phrase *revolutionary design* should only be used when device uses a new physiologic principle to restore continence. Hence tapes would be different from the artificial urinary sphincter, which would be different from intramural urethral bulking agents. An attempt has been made to define different classes of operations and devices for the treatment of SUI [3]. Within the category of tapes, there are retropubic tapes such as the tension-free vaginal tape and there are transobturator tapes. The single-incision tape can be put in using either of these principles, depending on the individual patient. These tapes all follow the same principle: to support the vaginal hammock. Hence one cannot be considered revolutionary with respect to the other. However clinicians would view these three types of tapes as sufficiently different that they would wish to see high-quality research to determine whether one has an advantage over another. When similar tapes are offered in the marketplace, the situation becomes more difficult. There are several different retropubic tapes that can be introduced from the vagina upwards or from the retropubic area downwards. To show a difference in the safety and efficacy between such tapes, assuming satisfactory tape material was used, would require a trial of enormous and unrealistic proportions. Hence postmarketing surveillance is essential to determine whether there were any unexpected adverse events or late failures when a new retro-pubic tape was introduced.

The role of the workshop was not to define the precise care pathway for women with SUI. However, there are other issues around the safety and efficacy of tapes in certain groups of women. There may be relative contraindications, and caution must be shown in all patients who have undergone previous pelvic or lower abdominal surgery, in particular where adhesions are suspected or where mesh has already been used (eg, in inguinal hernia repairs). In addition, patients who have a congenitally distorted pelvis or in whom the pelvis has been traumatised by other causes (eg, trauma, radiotherapy, or surgery) must have a more detailed assessment and, in some cases, specialised imaging

before they undergo any SUI tape procedure. The precise, relative contraindications remain to be defined.

10. Conclusions

The clinicians at the meeting concluded that all parties need to ensure that they fulfil their obligations to optimise patient safety and to ensure that patients only receive devices that are likely to produce a significant improvement in their incontinence and to deliver a satisfactory quality of life. The key points to improving the current situation when a new device is introduced into the market are as follows:

- Adequate clinical evidence should be available to support its safety and efficacy.
- A standard for training and mentorship for the use of a significantly new device should be produced by the professional organisations.
- A register should be established or a formal systematic postmarket surveillance programme introduced when a new device is introduced so safety and efficacy can be judged when the device is used by the wider surgical community.
- Surgeons should be reminded of the MHRA reporting system, particularly when a new device is introduced; a “red card” system should be seriously considered.

Although the workshop was held in the United Kingdom and refers to the UK regulator and to UK professional bodies, devices are marketed worldwide, and the regulations for devices emanate from the European parliament. Hence the recommendations in this paper can be equally relevant to the whole of Europe and beyond.

Conflicts of interest: Paul Abrams took part in an AMS-sponsored symposium on postprostatectomy incontinence. Christopher Chapple has advised AMS on a new treatment for prostatic obstruction. Anthony Smith is taking part in a randomised controlled trial with a Boston Scientific mini tape, but the study has no financial input from the company. The company paid for travel expenses for the surgeons involved in the trial to receive training in the technique. The remaining authors have nothing to disclose.

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