Opinion and report on the equivalency of alternative products to intestines of animal origin for use as surgical sutures adopted by the Scientific Committee on Medicinal Products and Medical Devices on 16 September 1998

EXECUTIVE SUMMARY

The SCMPMD was asked to provide an opinion on the equivalency of alternative products to intestines of animal origin for use as surgical sutures. Specifically the Committee was asked for an opinion on whether such alternative products represent an equivalent or satisfactory alternative to catgut in relation to safety and performance. Moreover the Committee was asked to specify under which conditions would it be acceptable to use animal tissues for the manufacture of sutures, taking in account that currently available inactivation procedures for viral and non-conventional transmissible agents may not be used as they adversely affect the mechanical characteristics and functionality of the suture.

The report of the Committee provides the opinion that there are sufficient synthetic alternative products to catgut suture that provide equal, or even better clinical performance than catgut and that there are no clinical indications for the preferred use of catgut. The Committee recognises that there has been a diminishing use of catgut sutures during the last decade, that the decrease is likely to continue and that there is, in fact, no further need for catgut sutures from the clinical point of view.

With respect to any continued commercial supply of catgut sutures, the Committee is of the view that, in the light of the bovine and ovine origin of the material, and the classification of intestines as tissues of medium infectivity,special conditions have to be met in order to manage the risks related to TSE. Since there are no known inactivation processes that can be applied to catgut, risk management cannot be achieved by this method. The Committee is of the opinion that risk management could only be addressed through the sourcing of material from BSE-free areas, coupled with the use of processing methods that involve a controlled system of collection and handling in order to prevent cross

contamination. Specifically, in the case of any continued production of catgut, the manufacturing process should be in conformity with the guidelines set forth in appropriate standards and guidance documents from the Commission.

The Committee draws special attention to the requirement within the regulatory procedure for medical devices for justification to be provided when using animal tissues in situations where satisfactory alternative materials are available. It is the opinion of the Committee that the Commission should specifically inform the relevant Competent Authorities and Notified Bodies of this point with the recommendation that all CE marked catgut suture products be reassessed in this light.

REPORT

Terms of reference

The Committee was requested by DG III of the European Commission to give a response to the following questions;

In the specific case of surgical sutures manufactured using intestine of animal origin (bovine and ovine), do the alternate products present an equivalent or satisfactory alternative in relation to safety and performance?

Under which conditions would it be acceptable to use such materials for the manufacture of sutures taking into account that currently available inactivation procedures for viral and non-conventional transmissible agents may not be used as they adversely affect the mechanical characteristics and functionality of the suture?

Background

The background to this request is that a wide variety of surgical sutures is currently available, including examples of both absorbable and non-absorbable materials, either of natural or synthetic origin, all of which have given perfectly acceptable performance for many years in surgical practice. Sutures themselves are not normally considered to be a risk factor in surgery and although there are differences between them in characteristics, they are all considered to be intrinsically safe. Catgut is a material derived from the intestines of either sheep or cows and has been used as an absorbable suture material for over a century. Until the

questions over transmissible infective agents related to the use of animal tissues in medical devices were raised in recent years, there have been no concerns over the biological safety of catgut. The question must now be raised, however, that if there is any risk of transmission of disease to surgical patients arising from the use of catgut, are there any alternative materials that may be used for all surgical procedures that currently employ catgut which have appropriate properties such that no patient would be disadvantaged or put to any greater risk? An analysis of these risks and risk / benefit ratios must take into account the changes to the properties and performance of catgut that would arise if the tissues from which it is sourced were treated with inactivation procedures for viral and non-conventional transmissible agents.

The Nature of Absorbable Suture Materials

Absorbable sutures are used for all surgical procedures in which deep layers of connective tissue have to be closed following trauma or surgery, where it is desirable for the material to degrade and be absorbed by the tissues of the body over time. It is imperative that the material retains its strength for a reasonable length of time (typically 14 - 21 days), such that the tissues are held together while wound healing takes place, and then resorbs over a further period of time, this usually being achieved within 6 months.

Absorbable materials may be either natural or synthetic. Catgut is the only significant example of a natural absorbable suture material in use today. It is a collagen-rich tissue derived from the submucosal fibrous tissue of sheep intestine or the serosal connective tissue layer of bovine intestine. The tissue is mechanically separated and cleaned, chemically treated to cross-link the collagen, typically with formaldehyde or chromium salts, and the resulting fibres are stretched and formed into a monofilament suture. The mechanical properties of catgut are ideal for most surgical applications. The rate of loss of strength varies from site to site depending on conditions, especially as the absorption process requires enzymatic activity (1), but typically the sutures will lose their strength over a 28 day period and will be completely absorbed within a few months (2). The tissue reaction to catgut is quite marked, with significant inflammatory cell activity associated with the material. This, however, is not considered detrimental to the wound healing process.

Synthetic alternatives to catgut have been available for over 20 years (3). There are several forms, all of the major varieties being made from

aliphatic polyesters, principally polyglycolic acid, co-polymers of glycolic and lactic acid and polydioxanone (4). These may be either monofilament or multifilament and between them provide a range of characteristics that cover all functional requirements for absorbable sutures. Most synthetic absorbable sutures degrade slightly slower than catgut, although some, for example those based on polydioxanone, have significantly slower degradation profiles. Most are also associated with a lesser inflammatory reaction. The degradation and absorption processes arise through hydrolysis and do not vary very much from site to site in the body.

A Comparison Between Catgut and Synthetic Absorbable Suture Materials

The following is an assessment of the relative merits of these two groups of material. It is emphasised that comparisons may be made both on firm objective grounds from scientific considerations, and also from an assessment of clinical merits and other factors, which may be more subjective but nevertheless have to be considered.

Mechanically there can be no doubt that synthetic suture materials can provide performance which is usually better than that provided by catgut and which at the very least is as good as catgut, with one exception mentioned below. By the very nature of the manufacturing process, synthetic materials are more consistent and reproducible in their quality and the batch to batch variation inherent in catgut is not seen. The range of strengths and absorption characteristics are entirely adequate for current surgical procedures. Moreover there are no surgical procedures which can be performed with catgut and which are inappropriate for synthetic sutures. On the contrary there are some procedures where the variability or unpredictability of the degradation of catgut, as pointed out by Tian et al (5) in the case of the stomach for example, makes it an inappropriate material. In terms of direct comparisons, Perey and Watier (6) found far better retention of strength with polyglycolic acid than with catgut, a conclusion also reached by Howes (7) who demonstrated slower and more consistent loss of strength with the polyglycolic acid and generally fewer complications. Postlethwait reported that two synthetic absorbable suture materials lost strength far more consistently than catgut in the stomach and duodenum (8) Herrman has published several papers in which the superiority of synthetic materials over catgut was reported with respect to the mechanical properties (9).

With respect to the tissue reaction, there is widespread agreement that there is usually less tissue reaction around synthetic sutures than around catgut. For example Wainstein et al have recently reported on the inflammation associated with catgut compared to several synthetic absorbable materials in a pyleoplasty model and found the most extensive tissue reaction with the catgut (10). This is consistent with many other observations in the literature. Whether a lower degree of inflammation gives better clinical performance is not always obvious. Bakkum et al (11) have shown differences in the inflammatory reaction to sutures placed in the peritoneum of rats, this increasing from synthetic non absorbable to synthetic absorbable and to catgut as expected, but could not see any correlation with clinical performance parameters such as post-surgical adhesions. On the other hand, Ketcham et al (12) have shown that the greater tissue reaction to catgut than to polyglycolic acid does give poorer clinical performance in the case of episiotomy repair, and Hanke et al (13) have shown reduced levels of cysts and other complications when synthetic sutures rather than catgut was used in the urinary tract. A contrary view has been expressed by Parivar et al (14), however, as they found better clinical results (shorter healing times and marginally fewer complications) when catgut was used in radical retropubic prostatectomy. Although not being able to demonstrate any histological differences between silk and catgut sutures, Kawakami et al (15) did show some functional neurological disturbances in an animal model of lumbar radiculopathy using chromic catgut which they associated with adverse effects of the degradation products of chromic catgut sutures on nerve tissue.

One of the main issues with catgut concerns infection. The degradation of catgut occurs much faster in infected sites, which could influence the clinical outcomes, whereas synthetic sutures are far less affected (16). Also catgut sutures appear to be associated with a greater risk of infection, possibly because of a greater degree of bacterial adhesion and the higher potential to serve as a focus for secondary infection (17). Tobin (18) has stated that ‘catgut sutures are a poor choice for use in contaminated wounds', and this position is consistently confirmed in the literature.

The one area where catgut does appear to have an advantage over synthetic materials is that of knot strength. Catgut is often considered easier to knot, and although this is not easy to quantify, knots do appear to hold well with less risk of slippage. There has been a subjective view in some places that this leads to less dehiscence although objective

studies such as that of Clark et al (19), in which 55% of catgut-closed colonic anastomoses showed evidence of dehisecence compared to 24% with polyglycolic acid sutures, tend to demonstrate the reverse. It is also a clinical impression that braided synthetic sutures have a greater tendency to tear through oedematous or fragile tissues or parenchymatous organs.

Clinical Preferences

As noted below, catgut sutures have become less and less popular amongst surgeons over the last decade. Ten years ago catgut comprised approximately 20% of the sale of sutures in Europe. This figure has now dropped to about 7% and there is a clear downward trend (20). Overall, probably less than 10% of surgeons use catgut routinely and the vast majority of these will be older surgeons who trained at a time when it was the only absorbable suture available. In most advanced countries all younger surgeons will exclusively use synthetic materials. In certain clinical disciplines, such as gynaecology, there is a strong opinion against the continued use of catgut.

Laufman and Rubel have discussed the preferences for absorbable suture materials with respect to individual properties and clinical speciality (21). In relation to abdominal operations they quote Haxton et al (22) who determined that because of the wound dehiscence and infection problems, the substitution of synthetic materials for catgut would lead to a much reduced incidence of complications. As reported by Blau et al (23), many ophthalmological procedures benefit from the availability of synthetics over catgut, for example in strabismus procedures. Similarly, polyglycolic acid sutures have been shown to be superior with respect to postoperative pain, oedema, infections and other complications in anorectal procedures such as hemorrhoidectomies (24). Chusak and Dibbell have also demonstrated the considerable superiority of polydioxanone in plastic surgery (25). There are many other reports in the clinical literature confirming the clinical superiority of the synthetic absorbable materials and it is not uncommon to see in authoritative textbooks on surgical technique over the last decade the statement that ‘there is little place for catgut in modern surgery' (26).

Manufacturing Considerations

processes, it would not be a straightforward matter for a manufacturer of catgut sutures with no previous synthetic suture products to change

production to synthetic sutures.

Transmissible Spongiform Encephalopathies in Relation to Catgut

Since catgut is derived from bovine or ovine intestinal tissue, questions concerning the risk of TSE and other transmissible infections have to be raised.

Because catgut sutures are placed in tissues where the vascularity is compromised, and since the catgut is totally absorbed, there is a strong possibility of systemic distribution of any infective agent present in the material. Therefore the use of the suture should be considered almost equivalent to a parenteral administration of a substance.

However, based on current knowledge, there is no indication of an association between TSE and catgut sutures.

In the risk assessment associated with this use, three principle factors have to be considered, the geographical origin of the source, the infectivity of the tissue in question and the possibility of inactivation. In addition, the quantity of material used in any one patient and, as noted above, the route of administration, may contribute to the risk of infection.

The issue of TSE risk in animal tissue is addressed in European standards (28) which deal with details of risk assessment, sourcing and inactivation.

As far as these three principle factors are concerned, the following points should be noted:

- Intestines are currently classified as tissues of medium infectivity.

- The current major sources are Australia and New Zealand, considered to be BSE - free according to the latest OIE information (28).

- As all inactivation processes cause severe changes to catgut, it is not possible to apply these methods to these sutures in order to eliminate infectious agents.

CONCLUSIONS AND RECOMMENDATIONS

1. The Committee considers that there are sufficient alternative products

to catgut sutures, i.e. synthetic absorbable sutures made from polymers such as polyglycolic acid, that provide equal, or even better, clinical performance than the catgut. Apart from considerations of TSE, there is no difference between these two types of sutures with respect to matters of safety.

2. On the basis of the considerations in the above clause, generally there are no clinical indications for the preferred use of catgut. Moreover, scientifically there is no further need for catgut sutures. The Committee recognises that there has been a diminishing use of catgut sutures during the last decade and that this decrease is likely to continue.

3. Based on considerations of the bovine origin and the classification of intestines as tissues of medium infectivity, special conditions have to be met in order to manage the risks related to TSE with catgut.

4. In the case of any continued production of catgut, the manufacturing process should be in conformity with the guidelines set forth in appropriate standards and guidance documents from the Commission, currently in prEN 12442 parts 1,2 and 3, and in MED.DEV 2.5/5 (29)

5. Since there are no known inactivation processes that can be applied to catgut, risk management cannot be achieved by this method. Risk management may only be addressed through the sourcing of material from BSE-free areas, coupled with the use of processing methods that involve a contolled system of collection and handling.

6. The Committee draws special attention to the requirement within the regulatory procedures for medical devices for justification to be provided when using animal tissue in situations where satisfactory alternative materials are available. The relevant Competent Authorities and Notified Bodies should be made aware of this with respect to the CE mark approval process for catgut sutures.

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