■ ASPECTS OF CURRENT MANAGEMENT

The use of fibrin glue in surgery of the knee

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Fibrin glue, also known as fibrin sealant, is now established as a haemostatic agent in surgery, but its role in orthopaedic surgery is neither well known nor clearly defined. Although it was originally used over 100 years ago, concerns about transmission of disease meant that it fell from favour. It is also available as a slow-release drug delivery system and as a substrate for cellular growth and tissue engineering. Consequently, it has the potential to be used in a number of ways in orthopaedic surgery. The purpose of this review is to address its use in surgery of the knee in which it appears to offer great promise.

History and development

Bergel[1] described the use of fibrin as a haemostatic agent in the form of a dry plasma powder over a century ago. In 1915, Grey[2] compared sheep fibrin with wet cotton and thought that "while fibrin probably exerts no appreciable chemical influence on the process of coagulation, it appears to possess some mechanical property favourable to the formation of a firm clot". A year later, Harvey[3] improved the preparation by converting it into a paper-like substance and plasticising it with heat. Fibrin then fell out of favour until 1940, when it was successfully used as an additional adhesive for nerve anastomoses; its use reduced the tension in the sealed stumps at the anastomosis site.[4,5] Development thereafter came to a standstill because of two distinct problems, namely, poor adhesion and transmission of disease. Some soldiers from World War II with severe burns were treated with skin grafts which had been partially stabilised with a thrombin and fibrinogen complex,[6] but these lacked adhesion because of an insufficient concentration of fibrinogen.[7,8] Furthermore, many patients acquired hepatitis because human fibrinogen was used.

In 1972, the technology was successfully reintroduced for peripheral nerve repair in animal models[9] and subsequently, in 1974, in man.[10] Concentrated fibrinogen was used with enhanced Factor XIII (fibrin stabilising factor) and aprotinin which prevented the premature degradation of the fibrin. The first commercially available fibrin glue was marketed in 1982, although approval by the Food and Drug Administration was not granted till 1998 which allowed Europe and Asia to lead the way in its evaluation.

Preparations

The classification of the various preparations is difficult. Some review articles have categorised them into natural and synthetic preparations. However since they all contain some manufactured ingredients, this is not appropriate. Most preparations convert fibrinogen to fibrin in a reaction catalysed by thrombin (Fig. 1). This allows them to be more suitably classed as either autologous or homologous glues depending on whether the fibrinogen comes from the patient's own plasma or from an alternative source. The main advantages of autologous fibrin glue are the reduced risk of transmission of disease and cost, although autologous blood donation may not be possible in severely injured patients or in unanticipated emergencies.[11]

Several authors have decribed making fibrin glue for surgical use themselves by extracting fibrinogen either from a single donor or by pooling plasma and then mixing it with calcium and bovine thrombin.[12-14]

The first generation of commercial glues (Tisseel/Tissucol; Baxter, Vienna, Austria and Beriplast; Centeon, Marburg, Germany) originally consisted of human fibrinogen and bovine thrombin plus bovine aprotinin which acted as an inhibitor to fibrinolysis. Viral transmission remained a risk with such constituents. This was reduced by careful screening of donors, heat treatment of the human fibrinogen component[15] and, ultimately, by the

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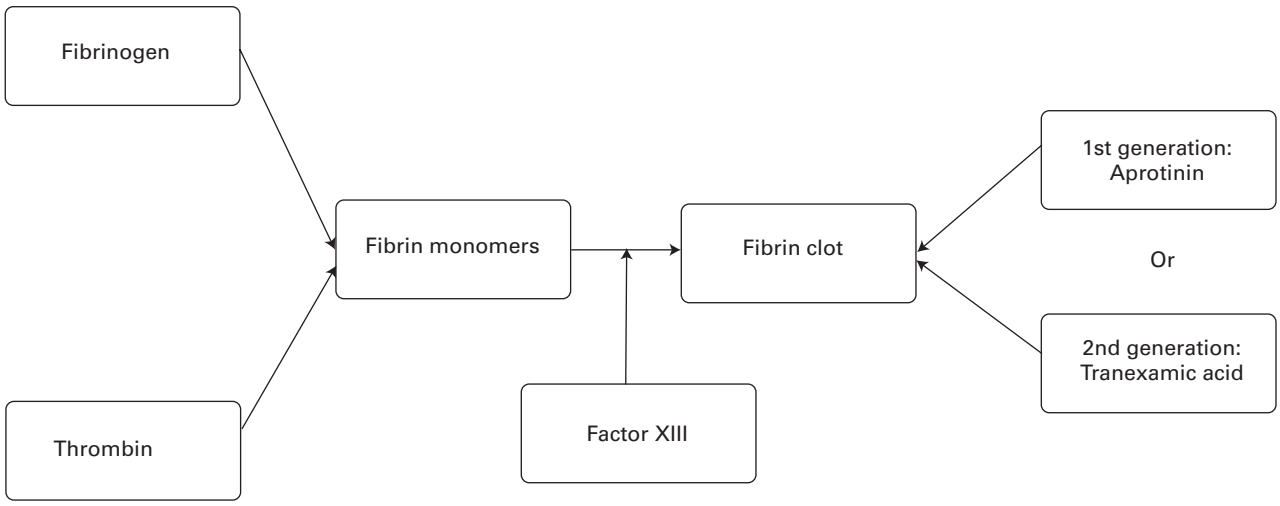

Fig. 1

Diagram showing the preparation of fibrin glue. It is made by mixing thrombin and fibrinogen. Most commercial preparations use an antifibrinolytic agent, the nature of which depends on whether it is a first- or second-generation product.

replacement of bovine thrombin with virally-inactivated human thrombin.[16] The desire to avoid any bovine products led to the development of a second-generation fibrin glue (Quixil; Crosseal; Omrix Biopharmaceuticals Rehorot, Israel) which replaced bovine aprotinin with tranexamic acid as the antifibrinolytic agent. Safety issues concerning tranexamic acid led the manufacturer to develop a modified version without the antifibrinolytic agent (Evicel; Omrix Biopharmaceuticals).

Commercial preparations of fibrin glue are available either in a frozen pre-mixed state which requires thawing before use or as separate constituents which require mixing. For the latter, constituents are placed in separate syringe tubes and mixed by connecting them together to a single lumen through which the glue is expelled. This can be through either a syringe (Fig. 2) or a high-pressure spray.

All the methods of preparation discussed so far have essentially involved mixing fibrinogen and thrombin to form fibrin glue. However, one other method is available. The Vivostat system (Vivolution A/S Alleroed, Denmark) is a technique which uses the patient's own blood to make purified fibrin I without the need for exogenous thrombin. A vial of the fibrin I solution is mixed with an alkaline carbonate/bicarbonate buffer on application. The buffer helps to increase the pH of fibrin I to neutral where, in the presence of calcium ions, endogenous prothrombin is converted to thrombin with two subsequent effects. First, the endogenous thrombin causes fibrinopeptide B to be cleaved from fibrin I to form fibrin II and, secondly, it activates endogenous Factor XIII. This acts upon the acid-soluble fibrin II polymer to form a chemically stable cross-linked fibrin II polymer.[17]

It should be appreciated that there are many more brands of fibrin glue available than have been mentioned. However, the aim of this paper is to familiarise the reader with the various types rather than describe each individual product.

Safety

In using any blood-derived product, consideration must be given to safety, especially in regard to allergy, anaphylaxis and transmission of disease. Anaphylactic reactions, including one fatality, have been reported in a few patients and attributed to aprotinin, a 6512-dalton bovine peptide found in some commercial fibrin glues.[18-22] A history of previous exposure to aprotinin was present in most, although not all the cases. Overall, the likelihood of an allergic or anaphylatic reaction from bovine aprotinin in a fibrin glue is 0.5 per 100 000 applications and 0.3 per 100 000 for a serious reaction.[23] By contrast, 2% of patients have a severe allergic or pseudoallergic reaction on re-exposure if it is given intravenously.[24] Consequently, the use of intravenous (IV) bovine aprotinin has now been withdrawn after it was seen to increase mortality in cardiac patients by up to 64%.[25] Tisseel replaced this bovine fibrinolytic inhibitor with a synthetic substitute in 2007 in the United States.[26]

In addition to the aforementioned aprotinin-related fatality, there have been two deaths from the use of Quixil which does not contain aprotinin. Both patients suffered severe neurotoxic reactions after the tranexamic-acid component came in contact with the dura mater and cerebrospinal fluid during neurosurgical procedures.[27]

Symptomatic viral transmission of human parvovirus B19 is well documented after the application of fibrin glue and has led to anaemia, neutropenia and aplastic crises.[28-34] Although there are no current reports following the use of fibrin glue in orthopaedic surgery, this is likely to be due to its infrequent use rather than to an increased susceptibility

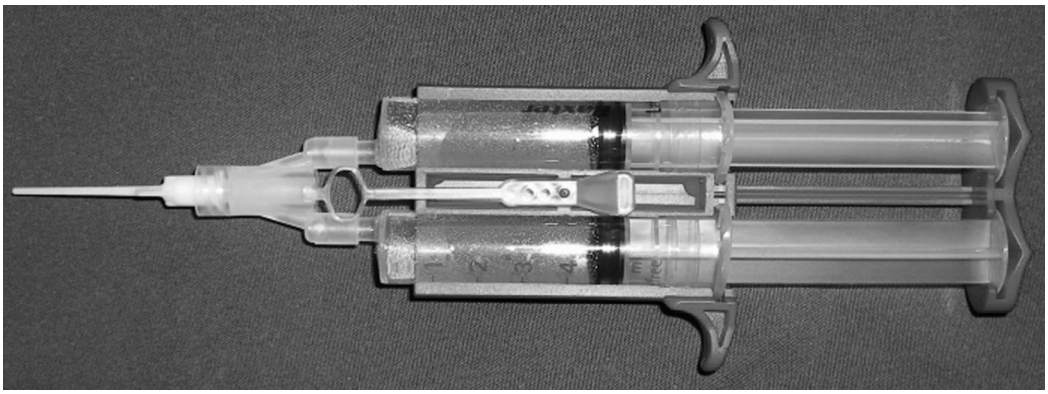

Fig. 2

Photograph of a dual-chambered syringe containing freeze-dried fibrinogen and pre-warmed aprotinin in one chamber, and freeze-dried thrombin and pre-warmed calcium chloride in the other. When the plunger is depressed the contents of both chambers are ejected through a single lumen thereby allowing the contents to mix.

to transmission of disease in other surgical specialties. Of greater concern both to the surgeon and patient is the risk of transmission of the human immunodeficiency virus (HIV) and hepatitis A, B and C (HAV, HBV and HCV, respectively). HIV transmission has been reported after the use of cryoprecipitated fibrinogen,[35] although this was before the implementation of strict haematological testing. The estimated risk of viral transmission per vial is less than 1 in 10^{15} for HIV, HAV, HBV and HCV for both fibrinogen and thrombin, 1 in 500 000 for parvovirus transmission per vial of fibrinogen and less than 1 in 107 per vial of thrombin. The increased risk of transmission is related to the increased prevalance of parvovirus in the population and its greater thermal stability.[36]

Current and experimental therapeutic targets

Fibrin glue is not yet used routinely in knee surgery. It is therefore necessary to consider areas in which it has been employed successfully and experimental studies which suggest possible advantages over current methods.

Total knee replacement. Advances in the design and fixation of implants have improved the survival and function of total knee replacement (TKR). Blood loss remains a considerable side-effect and it has been estimated that over 1400 ml are lost after each procedure, although much of this is occult.[37,38] Steps to reduce this loss and the consequent need for transfusion include the systematic administration of tranexamic acid,[39,40] the local infiltration of epinephrine[41,42] and clamping of the drains to tamponade the joint cavity.[43,44] These are not always effective.[45-47]

Fibrin glue may be useful in these circumstances by acting as a sealant to provide haemostasis. In 1997, Akizuki, Yasukawa and Takizawa[48] described coating the surfaces of cancellous bone with fibrin glue before insertion of the implants. This was followed by an injection of carbazochrome sodium sulphonate and tranexamic acid into the knee at the end of the operation in addition to clamping of the drain for 30 minutes after release of the tourniquet. They reported a mean total blood loss of 235 ml after unilateral TKR and of 402 ml after bilateral TKR. However, this was an observational study with no control group. Despite this, it is worth noting that the blood loss was much lower than would normally be expected and that no patient required transfusion. It should be emphasised that both ingredients of the intra-articular 'cocktail' given at the end of the operation were haemostatic agents and therefore the reduction in blood loss could not solely be attributed to the fibrin glue.

In 1999, two studies were published which described the use of fibrin glue, one in animals and one in men. Curtin et al[49] performed bilateral knee surgery in nine dogs using one limb as the test side and the other as the control. The surgery performed was identical to TKR with the exception of prosthetic implantation. Quixil (which contains tranexamic acid) was sprayed after all bone cuts and soft-tissue releases were made. A considerable reduction in the mean total blood loss was noted, 470 ml in the treated joints against 1005 ml in the control joints ($p < 0.05$). In addition, as blood loss from the control joint increased, the effectiveness of the fibrin glue became more apparent. Although the authors suggested that fibrin sealant would reduce bleeding after TKR, they did not actually implant the prosthesis which may in itself limit bleeding from the prepared surface of the cancellous bone. Of greater clinical interest that year was a study by Levy et al[50] who also used Quixil, but in patients undergoing TKR. They studied 58 patients with osteoarthritis of the knee and randomised them into two groups, with and without fibrin sealant. After implantation of the prosthesis the entire operative field was thoroughly rinsed of any debris and meticulously dried before closure of the soft tis-

sues. The fibrin glue (10 ml to 20 ml) was then applied by topical spraying using a double-syringe spray-device over the tissues, into the joint itself, on the raw surfaces of the bones, on the muscles and tendons and around and on the subcutaneous tissues, while all of the so-called hidden pouches of the joint were exposed in order to cover as much of the surface area as possible with a film of glue. The calculated blood loss was significantly lower in the fibrin sealant group (1063 ml *vs* 1768 ml, $p < 0.001$) with a corresponding reduction in both the number of patients requiring transfusion (5 *vs* 16, $p = 0.004$) and the total number of units transfused per group (6 *vs* 24, $p < 0.001$).

Their findings were supported by a study on fractures from a different institution in which 10 ml of Quixil was sprayed on to the raw surfaces of exposed bone and soft tissue after cementing of the joint, and before deflation of the tourniquet and closure of the wound.[51] The mean drainage over 12 hours post-operatively was 56% less in the fibrin sealant group than in the control group ($p = 0.002$), but while there was a trend towards an increasing requirement for transfusion in the control group, it did not reach significance. A follow-up study from the same group showed that the blood loss differed if patients were grouped into those operated on in the early part and those in the latter part of the study.[52] The decrease in post-operative haemoglobin 48 hours after TKR was 3.5 g/dl in the early control group and 3.25 g/dl ($p = 0.34$) in the early fibrin glue group. The comparable figures in the late group were 3.53 g/dl in the control group and 3.01 g/dl in the fibrin glue group ($p = 0.04$) suggesting that experience is an important factor for successful application of fibrin glue.

The current interest in the use of intravenous tranexamic acid to reduce blood loss makes it a pertinent substance against which to compare the use of fibrin glue. Molloy et al[53] randomised 150 patients into three groups, a control group, a group which had Quixil (which contains tranexamic acid) sprayed on the wound and a group which received IV tranexamic acid. The mean blood loss for the control group was 1415 ml, the Quixil group 1190 ml and the IV tranexamic acid group 1225 ml ($p = 0.016$ and 0.041). The reduction in blood loss was statistically significant when compared with the control group although there was no difference between both test groups ($p = 0.72$). The evidence to date has shown that fibrin glue is effective in reducing blood loss after TKR although it is likely that IV tranexamic acid is a more viable long-term alternative because it is easier to administer and not prone to variable application.

A combination of fibrin glue and platelet gel may be the method by which fibrin glue makes its mark in TKR. Platelet gel, which containts both concentrated platelets and their growth factors, is believed to improve wound healing although it has also been shown to have useful haemostatic qualities.[54] Everts et al[55,56] compared the outcome of this combination in 85 patients with 80 controls undergoing unilateral TKR. Autologous platelet gel and fibrin glue were manufactured intra-operatively by centrifuging a sample of the patient's own blood to separate it into platelet-poor plasma, platelet-rich plasma and leucocytes and erythrocytes. Autologous thrombin was used for most of the patients (n = 72). Bovine thrombin was only used when it was not possible to produce a sufficient quantity (n = 13). The fibrin glue and platelet gel were introduced after the implant had been inserted. Initially, 10 ml of platelet gel were injected in the back of the knee cavity, the posterior recess, the gutters and the raw exposed surfaces of the femur and tibia and this was followed by an application of fibrin glue over the wound. After the knee capsule had been closed, a further 10 ml of platelet gel were injected between the stitches of the repaired extensor mechanism and the prepatellar bursa, and fibrin glue was again sprayed over the wound. The control patients received a drain while the test subjects did not since the authors argued that platelet gel may be lost through the drain. The post-operative haemoglobin levels at 24 hours were much higher in the test group (11.3 g/dl *vs* 8.9 g/dl, $p < 0.001$) although benefits other than that of better haemostasis were also noted. There were, for example, no cases of superficial wound infection in the test group, but four occurred in the control group ($p < 0.05$). The hospital stay was shorter in the test group (6.9 days *vs* 8.3 days; $p < 0.001$), the range of movement on the fifth post-operative day was greater (92° *vs* 79°; $p < 0.001$) and the incidence of arthrofibrosis was lower after five months (10% *vs* 2%; $p < 0.001$). It is unlikely that these benefits could be attributed to the fibrin glue rather than the platelet gel, although it is possible that the presence of the glue helped to keep the gel at its target site.

It appears that fibrin glue could have a role to play in TKR, but its use in the near future is likely to be limited to patients who are intolerant of IV tranexamic acid or to high-risk patients such as those with haemophilia.[57]

Injuries of articular cartilage. The outcome of treating an injury to the articular cartilage is dependent on the surgeon, patient and the lesion itself. Injuries can range from a discrete osteochondral defect to a fracture extending into the articular surface. Fibrin glue has an established place among the second-line treatments available for osteochondral defects after microfracture and abrasion chondroplasty, although experience of the use of fibrin glue to treat large chondral fractures around the knee is limited.

In the early 1980s, fibrin glue was used as an adhesive to secure post-traumatic chondral and osteochondral loose bodies. Kaplonyi et al[58] reattached nine fragments to the lateral femoral condyle and six to the medial facet of the patella using fibrin glue alone. The total cohort of 28 patients included those with reattachments at other sites. While follow-up was somewhat haphazard, nine of the 12 joints which underwent arthroscopy had normal joint surfaces and 14 of the 15 with radiological follow-up had united. This method has since fallen out of favour since internal fixation is perceived to be more reliable.[59]

Table I. Details of the outcome of the use of fibrin glue and additional factors in the healing of meniscal tears in animal models

Author/s	Model	Meniscal tear	Test groups	Review time (wks)	Outcome
Roeddecker et al[68]	*In vivo*, rabbit	Longitudinal incisions in the posterior horn of the medial menisci	Control *vs* suture *vs* fibrin glue	6	Histology of fibrin group equal to the control; sutured group had thinner scar tissue and better vascularity
Ishimura et al[69]	*In vivo*, rabbit	1.5 mm full-thickness defect in the avascular zone	Control *vs* fibrin glue *vs* fibrin glue and marrow cells	12	Earlier mature healing and smaller defects in fibrin groups. Effect enhanced by marrow cells
Izuta et al[70]	*In vitro*, rat	1.2 mm full-thickness defect in the anterior horn	Control *vs* fibrin glue *vs* fibrin glue and MSC	12	No extracellular matrix invasion of the defect in the controls group; invasion in 25% of samples with fibrin glue; invasion in 75% of samples with fibrin glue and MSCs
Hashimoto et al[71]	*In vitro*, dog	2 mm full-thickness defect in the avascular zone	Control *vs* fibrin glue *vs* fibrin glue and ECGF†	24	Increased connective-tissue filling in fibrin glue groups; effect enhanced by ECGF (5% *vs* 77% *vs* 89%)
Scotti et al[72]	*In vitro*, transplanted porcine menisci into nude mice	Meniscal slices with interposition of test substance	Fibrin glue *vs* fibrin glue and chondrocytes	4	Evidence of bridging only evident in fibrin glue and chondrocytes group

* MSCs, mesenchymal stem cells

† ECGF, endothelial cell growth factor

Fibrin glue is used extensively in all forms of autologous chondrocyte implantation (ACI). In its simplest form ACI involves the harvesting of chondrocytes and growing them *in vitro*. They are then held within a chondral defect by a covering collagenous or periosteal membrane which is sutured to the edges of the defect and sealed with fibrin glue. Matrix autologous chondrocyte implantation (MACI) is a later development which involves seeding the chondrocytes on to a matrix. This theoretically reduces the leakage of chondrocytes, saves time by requiring only a small incision and allows fixation exclusively with fibrin glue.[60] Although fibrin glue has no osteo-inductive properties,[61-63] it may promote migration and proliferation of human chondrocytes[64] and thus has advantages in addition to that of being a sealant. Indeed, the transformation of fibrin glue from a liquid to a solid material which allows the biosynthesis of cartilage has been achieved by mixing it with cultured chondrocytes and allowing the mixture to harden within defects (Chondron, Sewon Cellontech Co., Seoul, South Korea),[65] although this method has yet to be compared with ACI or MACI.

Meniscal tears. These are common but problematical since they are associated with progressive joint degeneration.[66] Meniscal repair, while being a viable alternative to meniscectomy in selected patients, is not universally successful and can fail even in the peripheral, well-vascularised zone. There is consequently some scope for the use of fibrin glue for meniscal tears, not only to keep the torn edges together but also to act as a scaffold for growth factors.

The longest reported follow-up of the use of fibrin glue to repair meniscal tears comes from Ishimura et al[67] who used Tisseel in 40 patients with 61 tears and followed them up for a mean of 8.2 years. The patterns of injury varied and included tears in all meniscal zones and bucket-handle tears. The heterogeneity and small size of the sample made it difficult to draw reliable conclusions, but the overall failure rate of 10% was comparable with that of modern techniques of meniscal repair. The factors associated with failure were supplemental sutures (50% failed), surgery less than three weeks after injury (24% failed) and insufficiency of the anterior cruciate ligament (20% failed). While bucket-handle tears (24% failed) and those in the white-white zone (20% failed) had a higher incidence of failure, these were not found to be independent causative factors. Given the technical difficulties of introducing glue into the knee percutaneously with arthroscopic assistance, it is not surprising that meniscal repair with its comparable failure rate is perceived to be a better option.

A possible role for fibrin glue which is currently being explored is as a scaffold for substances that promote meniscal healing. The results of using marrow cells, endothelial cell growth factor or mesenchymal stem cells (MSCs) incorporated into fibrin glue and then applied to tears of the avascular zone of animal menisci are encouraging.[68-72] However, human studies are still awaited (Table I).

Rupture of the anterior cruciate ligament. Since the 1980s fibrin glue has been suggested as an adjunct to the treatment of ruptures of the anterior cruciate ligament

(ACL).[73] However, the success of techniques of reconstruction using the hamstrings or a bone-patella-bone graft has meant that the early reported clinical success of ACL repair[73,74] is of little relevance today. Furthermore, recent evidence has shown that the application of commercial fibrin glue to an ACL repaired with sutures reduces the amount of organised collagen from 70% to 30%[75] which would inevitably have a deleterious effect on the ligament. The use of fibrin glue is currently directed at improving the quality of the graft and its integration wth the host.

To date, two substances which use fibrin glue as a transport medium have been investigated, namely, transforming growth factor (TGF)-β1 and MSCs. The former stimulates the proliferation of fibroblasts and enhances collagen synthesis in ligament healing and bone ingrowth[76] while the latter enhance tissue healing and tissue bioengineering in general.[77] Yamazaki et al[78] compared an untreated tendon graft with one treated with Bolheal (Kaketsuken, Kumamoto, Japan; aprotinin containing fibrin glue) and another treated with Bolheal and recombinant TGF-β1 in dogs. The presence of fibrin glue alone increased the pull-out strength of the graft although the effect was only marginal. By contrast, the addition of TGF-β1 nearly doubled the pull-out strength. On histological examination, perpendicular collagen fibres resembling Sharpey's fibres were seen connecting the tendon to the bone. Similar biomechanical findings have been demonstrated using fibrin glue and MSCs.[79,80] Of interest is the different histology reported in the studies using MSCs. Both Lim et al[79] and Soon et al[80] noted that tendon grafts treated with MSCs healed with a zone of fibrocartilage containing type-II collagen. This is a method of healing that occurs with the use of bone-patella-bone grafts and therefore may be more physiological.

This limited evidence does not allow any conclusions as to whether TGF-β1 or MSCs using fibrin glue as the transport medium has greater potential, but studies on them are justified to determine if these findings can be translated into improved clinical outcome.

Benign cystic tumours. Fibrin glue has been used successfully on the treatment of haemophilic pseudotumours[81] and synovial cysts around the knee.[82] This technique involves aspiration of the cyst followed by injection of fibrin glue. The glue seals off the neck of the cyst or tumour thereby preventing recollection. Although there is lack of long-term studies, the initial reports are encouraging[81,82] and it is surprising that this technique has not been used more widely.

Fibrin glue has been shown to be effective in a number of clinical situations and has scope for further development. It is our belief that, with the exception of chondrocyte transplantation, it is at present under-used as an adjunct to surgery of the knee. The challenge is for future research to determine if the experimental applications discussed can bring clinical success.

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