

The Vivostat[®] application system: A comparison with conventional fibrin sealant application systems

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Abstract. The method of applying fibrin sealants may affect their physical properties and surgical performance. In this study, the characteristics of a novel fibrin-sealant application system (Vivostat[®]) were compared with conventional fibrin sealant spray systems. Delivery rates of Vivostat were highly reproducible in both high and low delivery modes (coefficient of variation [CV] < 1.0%). Airflow rates of Vivostat were 578 ml/min (6.6% CV) and 688 ml/min (6.5% CV) at the high and low delivery modes, respectively; these were lower and less variable than conventional systems, which ranged from 5,000 to 10,000 ml/min depending on the pressure. Spray forces of Vivostat were consequently lower than other systems and the deposited fibrin films formed were of more consistent thickness. Unlike other systems, blockages with Vivostat were rare on intermittent use. The Vivostat system offers the surgeon a controlled, precise and efficient means of fibrin sealant application with potential performance advantages over conventional spray application systems.

Keywords: Vivostat[®], fibrin sealant, application, spray

1. Introduction

Fibrin sealants are widely used to achieve haemostasis and to seal air and fluid leaks in a wide variety of surgical procedures [2,3]. They are generally applied as two components (fibrinogen and thrombin solutions in conventional systems) that are mixed simultaneously on delivery to the surgical site, whereupon they polymerise rapidly to form a fibrin gel. The method of mixing and application is important as this can directly affect the physical properties and clinical performance of the sealant [13–15]. Spray application is often the preferred method [12–14,16].

The ideal fibrin sealant application system should provide efficient component mixing, a reproducible and controlled delivery ratio and precise dosage control. It should be cost effective and employ appropriate delivery rates to minimise fibrin sealant wastage. It should enable the sealant to be applied as an efficacious film of the required thickness at close range to the target tissues without risk to the patient. It

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Fig. 1. A conventional fibrin sealant spray application system (Duploject[®]) as used with Tissucol[®]. The rate of delivery is controlled by simultaneous manual depression of the syringe plungers.

should also be possible to use it intermittently with a low incidence of blockage. Finally, the application system should have a user-friendly design, preferably permitting one-handed or fingertip operation.

Most conventional fibrin sealant application systems are of simple design. They generally consist of two syringes, one containing thrombin solution and the other fibrinogen solution, which are delivered to the surgical site using various techniques depending on the indication and the preference of the surgeon. Three methods of application are commonly used: sequential layering, simultaneous application, and spray application. Sequential layering involves addition of the fibrinogen component followed by an equal volume of the thrombin solution direct to the surgical site. Simultaneous application of fibrin sealants involves applying the two components together through a needle or catheter. Spray applications involve applying fibrin sealant through a spray tip or an air-driven spray head, typically attached to an airline plugged directly into the hospital air supply. The Duploject[®] spray used with Tissucol[®] is shown in Fig. 1. Although there are specific situations where all three techniques can be used successfully, sequential and simultaneous techniques have been shown to be inferior methods of sealant application in comparison with spray techniques that produce the best fibrin sealant in terms of structure, efficacy and minimum wastage [13].

The Vivostat[®] system (Vivolution A/S, Birkerød, Denmark) is a novel, fully automated medical device for the preparation and application of patient-derived sealant [4–6]. Vivostat is currently available in Europe but is not currently approved or available for use in the US. Unlike other fibrin sealants, which utilise fibrinogen, thrombin and other auxiliary proteins from pooled human or animal sources, all protein components of the fibrin gel in Vivostat sealant are derived from the patient's own plasma. Thus, with Vivostat, there is no risk of transmitted infection from pooled plasma sources. The Vivostat system produces a purified concentrated fibrin I solution from 120 ml of the patient's blood. This is applied with a pH 10 neutralising solution in a 7:1 ratio to produce fibrin sealant. The Vivostat application system has a highly evolved electromechanical design incorporating a reusable applicator (Fig. 2), which houses the mechanical and electronic workings of the system, and a disposable, single-use Spraypen[®] (Fig. 3). On finger activation of the pen button fibrin I and neutralising solution are delivered at a controlled rate through separate tubes of a multilumen tube to the tip of the Spraypen; on emission from the tip they mix and are atomised in a stream of compressed air to form a fine low pressure spray of fibrin sealant (Fig. 4). The Vivostat application system was designed to be a convenient and effective surgical tool, offering more consistency of performance and ease of use than conventional spray systems.

This study was undertaken to compare key, and potentially clinically important, performance parameters of the Vivostat application system with those of conventional fibrin sealant spray application



Fig. 2. The Vivostat[®] Applicator. This fully automated device houses the syringes containing the fibrin and pH 10 repolymerising solution. On activation of the Spraypen[®] button these solutions, together with compressed air flow through a multilumen tube to the Spraypen (shown attached to the Applicator).

systems.

2. Materials and methods

2.1. Preparation of fibrin sealants

Fibrin I solutions were prepared from freshly donated whole blood or fresh frozen human plasma, using the Vivostat automated processor. This process took approximately 30 minutes, resulting in a syringe of fibrin I solution, the precursor to Vivostat sealant, at a pH of approximately 4.4. The fibrin I syringe and a syringe of pH 10 neutralising solution were connected to the Spraypen and loaded into the applicator. Fibrin sealant was delivered as a spray by activation of the Spraypen button.

Commercial fibrin sealant kits (Tissucol[®] [Baxter-Immuno, Austria], Beriplast[®] [Aventis Behring, Germany (EU) and Japan (JP)], and Bolheal[®] [Teijin, Japan]) were prepared in accordance with the manufacturers' instructions and applied using the corresponding syringes and spray tip (for Beriplast EU only) or air-driven spray heads provided (all other conventional systems). Tissucol and Beriplast JP were applied at pressures of 1.5 to 2 bar (150 to 200 kpa) from distances of 10 to 20 cm. Bolheal[®] fibrin sealant was applied at pressures of between 0.75 and 1 bar (75 and 100 kpa) from distances of 2 to 2.5 cm.



Fig. 3. The Vivostat Spraypen[®]. The fibrin sealant application is activated by finger depression of a button on the side of the Spraypen[®].

2.2. Assessments

The reproducibility of the Vivostat application system was assessed in terms of delivery rate, airflow and spray forces, cone angle, spray targeting, fibrin film thickness and the occurrence of blockages during intermittent use.

Delivery rates were assessed by spraying sealant into containers covered with polyethylene film (to prevent losses by splashing) for a period of 30 seconds. The container and polyethylene film were weighed pre- and post-delivery to determine the amount of sealant delivered. The airflow rates through Vivostat Spraypens were determined using a flow calibrator (Field-Cal 650, Humonics). The force of air generated by the spray application was assessed by fixing the Spraypen at set distances of 5 and 10 cm from a top pan balance and measuring the weight registered by the balance when air was applied from the Spraypen. Conventional application systems were assessed in the same way.

For targeting experiments, known volumes of Vivostat sealant of between 0.14 and 0.58 ml were applied from a set distance of 5 cm onto polyethylene film sheets of 2 cm² and 4 cm². Volumes of Tissucol, Beriplast, and Bolheal ranging from 0.10 to 0.84 ml were applied to the same targets using pressures and distances recommended by the manufacturers.

Fibrin film thicknesses for Vivostat and commercial sealants were measured using a fibrin profiler (N E Holm A/S; Birkerød, Denmark). In this method the surface profile of the fibrin sealant is detected using conductance by the tip of a needle. Volumes of 0.4 ml of Vivostat and commercial sealants were individually sprayed onto a metal plate and thickness measurements were taken across the centre of each clot.

For Vivostat, the incidence of blockage during the intermittent use was evaluated by spraying 0.3 ml of sealant with 90-minute dwell times throughout periods of up to 17 hours. Volumes of 0.2 ml of the

Table 1
Delivery rate of fibrin sealants: Time to deliver 1ml of sealant

Fibrin sealant	Syringe driving method	Spray activation method	Syringe sizes	Time for delivery (sec)	
				Mean	SD
Vivostat Low (0.7 ml/min)	Automatic	Air	5 ml/1 ml*	85.71	0.01
Vivostat High (0.4 ml/min)	Automatic	Air	5 ml/1 ml*	43.48	0.01
Tissucol	Manual	Air	2 ml/2 ml	5.84	0.73
Tissucol	Manual	Air	1 ml/1 ml	16.63	2.69
Beriplast (EU)	Manual	Manual	5 ml/5 ml	4.84	1.29
Beriplast (JP)	Manual	Air	5 ml/5 ml	3.70	1.16
Bolheal	Manual	Air	5 ml/5 ml	9.29	5.40
Bolheal	Manual	Air	1 ml/1 ml	6.53	1.37

conventional fibrin sealants were sprayed at time zero, 1, 5, 15, 30, 60, 120 minutes and 8 hours, reflecting time periods of possible use in a clinical situation. The ability to spray sealant using each application system after each dwell period and the effects on sealant characteristics were monitored. Further blockage data were also obtained from the use of conventional application systems when measuring other parameters.

Mean values and standard deviations were calculated for the data and the reproducibility was expressed as the percentage coefficient of variation (CV).

3. Results

3.1. Delivery rates

Delivery rates of the Vivostat System, assessed with the low (0.7 ml/min) and high (1.4 ml/min) settings, were measured as 0.70 ml/min (0.91% CV) and 1.38 ml/min (0.46% CV), respectively. Delivery rates of commercially available sealant application systems were found to be less well controlled, varying from 0.8 to 21.6 ml/min depending on the operator. From these data, delivery rates were identified that gave good spray quality. These ranged from 4 to 17 ml/min, depending on the application system tested. The delivery rates were then used to calculate the spray time of a specific volume of sealant (Table 1).

3.2. Air flow and force

The Vivostat airflow was recorded as 578 ml/min (6.6% CV) at the high delivery rate and 688 ml/min (6.5% CV) at the low delivery rate. Using the high delivery rate, the force of air at the target site when applied from 10 cm was 4.0 mN (4.9 mN using the low delivery rate). The Tissucol[®] system, by contrast, applied fibrin sealant with an airflow of between 5,000 and 10,000 ml/min, depending on the air pressure setting. This resulted in a force of 88 mN at the target site when sprayed from a distance of 10 cm and at a pressure of 2.5 bar (250 kpa), as for the low delivery rate of Vivostat (Fig. 5).

3.3. Efficiency of application to a target

Mean values of targeted Vivostat sealant from a set distance of 5 cm were 73.4% and 81.8% for 2 and 4 cm² targets, respectively. Targeted sealant volumes for conventional application systems were always less than Vivostat; in one case (Tissucol, 2 cm²) the quantity deposited on the target was as low as 9.1% (Fig. 6).

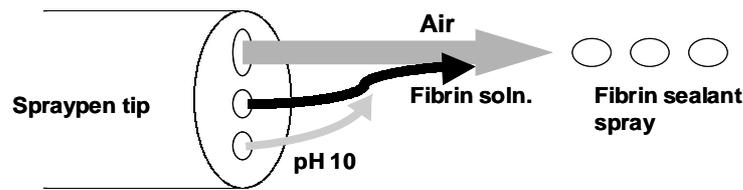


Fig. 4. Formation of a fibrin sealant spray at the tip of the Spraypen[®]. The fibrin I solution and pH10 buffer are emitted at a constant rate in a volume ratio of 7:1, whereupon they are drawn into the compressed air flow and atomised to form a fibrin sealant spray.

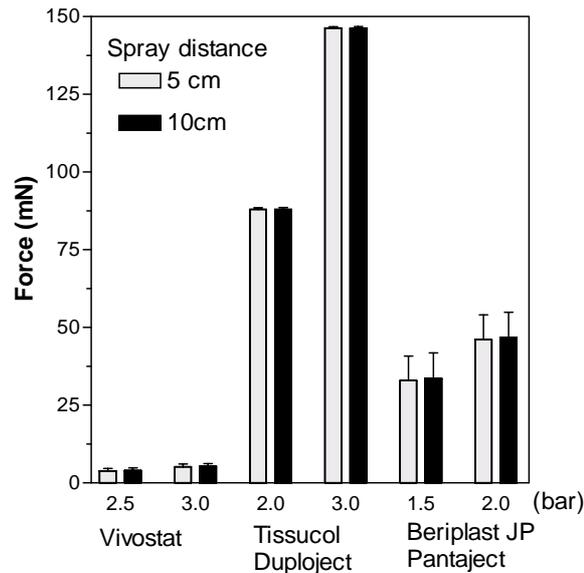


Fig. 5. Spray forces of Vivostat[®] and conventional fibrin sealant application (s.d. error bars) when applied at a distance of 5 or 10 cm.

3.4. Fibrin film thickness

0.4ml clots of Vivostat were always markedly thicker than commercial fibrin sealants (Fig. 7). The appearance of an indent in the centre of the Bolheal[®] samples is attributed to the close recommended spray distance (2 to 2.5 cm) and the relatively high air pressures of 0.75 to 1 bar (75 to 100 kpa), causing displacement of the sealant.

3.5. Blockage during intermittent use

For Vivostat, there were only two incidences (1.2%) of blockage from 174 spray applications, with both blockages seen 3.5 hours after initially loading the sample into the applicator. Incidences of blocking with other application systems were much higher. Beriplast (with the non-air driven spray tip) blocked every time spraying was arrested or if the delivery rate used was too slow. Other blockage rates were: Tissucol[®] 22.6%; Tissucol[®] DUO 23.6%; Beriplast[®] JP 20.0%; Beriplast EU, 81.3% and Bolheal[®], 30.5%. Data are summarised in Fig. 8; blockages have been classed as 'type 1' (recoverable with replacement of one or more components of the application system, always resulting in fibrin sealant

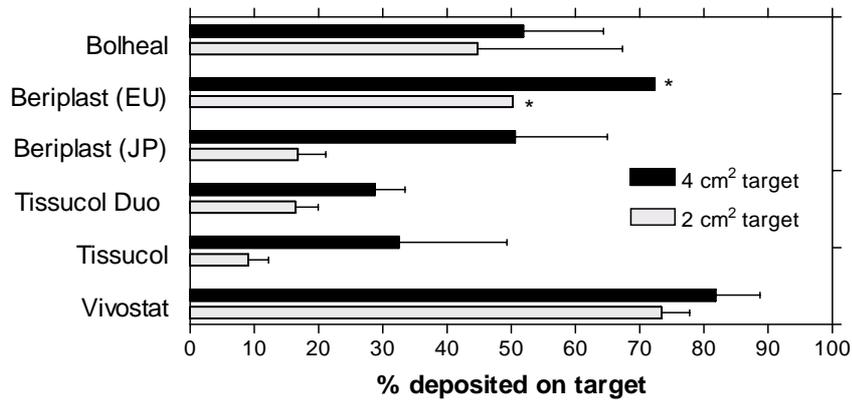


Fig. 6. Efficiency of spray deposition of Vivostat[®] and conventional sealants (s.d. error bars). The Vivostat[®] high settings was used. *There was only one test result for Beriplast EU.

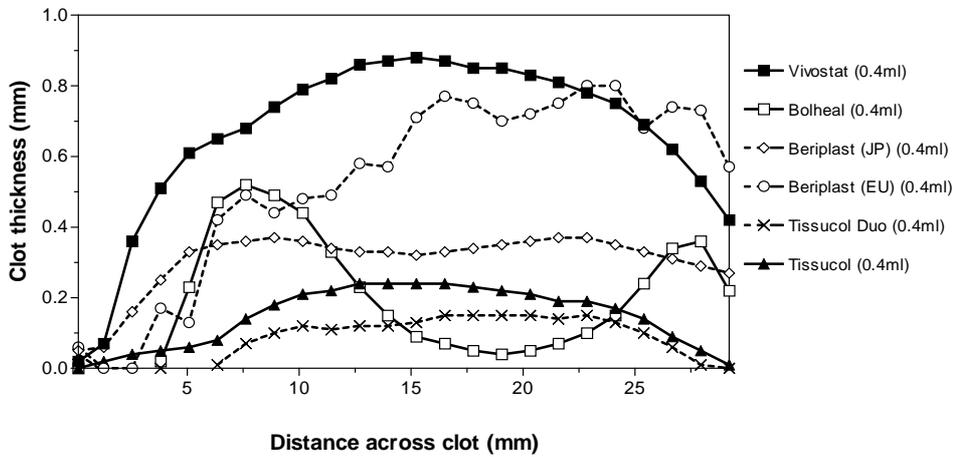


Fig. 7. Comparison of fibrin sealant thickness when sprayed at a distance of 4 cm.

wastage) and ‘type 2’ (self recovering/ recoverable by wiping, usually resulting in a poor spray and fibrin sealant wastage).

4. Discussion

The method of application can potentially affect the efficacy and safety of fibrin sealants. The key performance features of an ideal fibrin sealant delivery system include reproducible and controlled delivery rates, low potential for blockage and efficient and targeted delivery to the intended site. Analysis of these parameters in this study showed the Vivostat System to have many potential advantages over conventional fibrin sealant application systems.

Air-driven spray systems have the advantage of producing a uniform thin layer of fibrin sealant, however the use of pressurised air as a propellant in the application of any surgical product to a wound site always incurs a potential risk of gas emphysema, tissue rupture and air embolism [9,10]. These complications are potentially life threatening and, as such, all manufacturers specify guidelines to

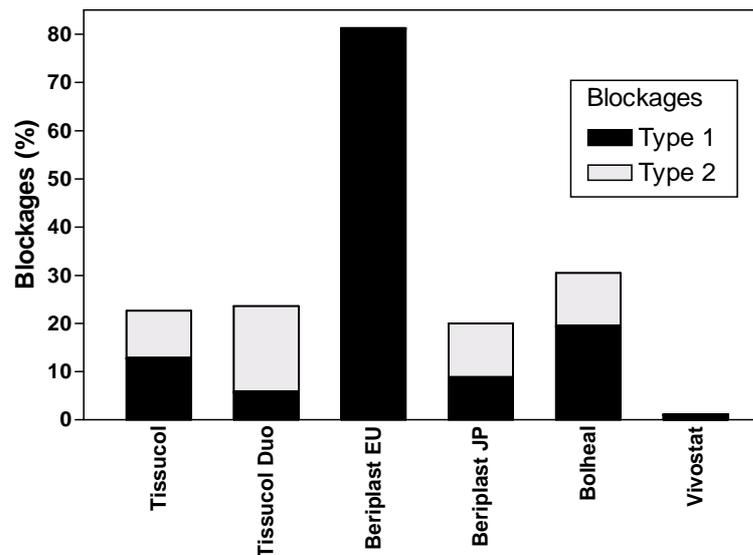


Fig. 8. Percentage blockages with Vivostat[®] and conventional fibrin sealant application systems. Type 1: Recoverable with replacement of one or more components of the application system, always resulting in fibrin sealant wastage. Type 2: Self recovering/ recoverable by wiping, usually resulting in a poor spray and fibrin sealant wastage.

minimise this risk (data on file, Baxter-Immuno AG, Centeon Pharma GmbH and Teijin Ltd) such as maximum pressures and minimum application distances. The Vivostat application system was designed to reduce such risks. The automated applicator has an integral air compressor and air pressures are precisely regulated at either 2.5 or 3.0 bar (250 or 300 kpa) according to the delivery rate selected (high: 1.4 ml/min and low: 0.7 ml/min, respectively). The recorded airflows (only 578 and 688 ml/min, in high and low flow mode, respectively) are far lower than those recorded with conventional sealant spray applicators. According to the manufacturer's instructions, the airflow exiting the Duploject(r) spray set is approximately 5,000–10,000 ml/min. Consequently, the forces generated by both the Tissucol and Beriplast systems are also far higher than those seen with Vivostat and explains the manufacturers' warnings of not using the application devices at close proximity. The lower spray forces seen with the Vivostat system compared with conventional application systems mean that the surgeon can apply sealant close to the wound site with a reduced risk of tissue damage or air embolism. Furthermore, the low spray forces reduce the possibility of disturbing the sealant layer as it is being applied. Measurements of delivery rate for Vivostat demonstrated close agreement with the nominal values with a high level of precision (CVs < 1.0%). The markedly lower delivery rates and spray forces of the Vivostat applicator allows more prolonged and controlled sealant application compared with conventional spray systems. In some cases where it is necessary to apply a large volume of fibrin in a short period of time, for example, in order to prevent rapid bleeding, the relatively low delivery rate of the Vivostat sealant (Table 1) compared with conventional sealants may be a disadvantage. This issue has been recognised by the manufacturers, who are already developing the system to allow a more rapid, yet still controlled, flow mode to cope with such eventualities.

Quantities delivered to a target area were higher with the Vivostat system than conventional systems. Possible explanations for the more efficient delivery of Vivostat are a lower degree of atomisation (i.e. fewer aerosol droplets), less splashback from the target resulting from the more rapid polymerisation and adhesive properties of Vivostat compared with other sealants [7].

Conventional application systems involving delivery through a needle or cannula frequently block on each dwell in application as the fibrin gel sets within the bore of the tube. Such blockages are difficult or impossible to clear and usually require a change of needle or cannula. Blockages were also seen in the present study when using the non air-driven spray tip supplied with the Beriplast EU kit. Air-driven spray heads show a reduction in blockage levels as mixing occurs outside the spray head. However, we have shown that these systems are still prone to blockage if used intermittently and left unused for periods over 1 hour. Such blockages always resulted in fibrin sealant wastage, and frequently resulted in no application of sealant, or the application of either the thrombin or fibrinogen component alone.

Intermittent use of fibrin sealant application systems with minimum blockages is seen as a great benefit as these blockages are both inconvenient to the surgeon and potentially costly if replacement spray sets are required. The results of this study, confirm the intended design of the Vivostat System to minimise the occurrence of blockages of the Spraypen during intermittent use. Should any blockages occur, they are usually on the tip and easily cleared by gentle wiping. Compared with other systems, less of the applied sealant is wasted and the majority of the sealant delivered is available at the wound site to perform the desired function.

Fibrin sealant films are considered to be beneficial in improving wound healing [1] and thin films, in particular, seem important in this regard [8,11]. Although thin film application is possible with conventional systems, the lack of dosage control means that varying amounts of fibrin sealant are wasted during spraying. In contrast, comparable film thicknesses can be produced when using less Vivostat sealant compared to other commercial sealants. These observations are reflected in the fibrin sealant profile data presented in this study.

Although the Vivostat application system offers several advantages over conventional systems, there are some limitations in the use of the Vivostat system as a whole that need to be considered by the surgeon. Firstly, the preparation of autologous Vivostat sealant requires the donation of 120 ml of blood from the patient undergoing surgery; although in most cases such a donation is of no consequence, in some situations (e.g. in small children) such a donation may be considered to compromise the patient's haematological status. Secondly, Vivostat sealant takes approximately 30–40 minutes to prepare. For situations in which the use of fibrin sealant was not envisaged prior to the operation, the use of Vivostat may not be appropriate. However, for elective surgery, the longer time for preparation of Vivostat is not problematic. Furthermore, even “off-the-shelf” conventional sealants can take from 15–30 minutes to reconstitute, depending on the product. Finally, the volume of sealant produced with the Vivostat sealant is variable from patient to patient (typically between 3 and 5 ml) depending on the fibrinogen concentration of the donated blood. In some cases larger volumes may be required: no such limitation applies to “off-the-shelf” conventional sealants. The limited volume of Vivostat sealant is, however, offset by the greater efficiency in use afforded by the application system and, in practice, the volume of Vivostat sealant is sufficient for most surgical procedures.

Spray application of Vivostat fibrin sealant applied to lung tissue has been demonstrated to be effective in preventing air leakage in a porcine animal model [5] and in reducing bleeding when applied to sternal marrow during cardiothoracic surgery [6]. Tissucol, Beriplast (EU) and Vivostat sealant (all sprayed) demonstrated broadly similar adhesive strengths in an *ex vivo* model using freshly excised human saphenous vein tissue, although the build up of adhesion was more rapid with Vivostat as a result of its faster polymerisation [7]. To date, however, there have been no published comparative trials *in vivo* of commercial fibrin sealants with which to confirm the potential performance advantages of the Vivostat application system demonstrated in the present *in vitro* studies.

While the present studies conducted in the controlled but somewhat artificial setting of the laboratory are of importance in comparing the basic characteristics of fibrin sealant application, it is recognised

that in clinical practise the situation in which fibrin sealants are used is very different. The tissues to which they are applied in surgery are extremely varied and as a result the optimal requirements for application will likely vary within and between operations. The good utility and performance of Vivostat is supported by field evaluations of in Europe. In these open, non-comparative trials, 61 surgeons used Vivostat in 307 diverse surgical operations and rated the performance of the sealant and the application system on a numerical scale from 1–5 (poor to excellent superior)(Vivolution A/S, data on file). The use of the Spraypen and the spray quality were both scored at 4 or 5 in 90% of cases. In 75% of cases the surgeons considered the system as being better overall than other fibrin sealant systems with which they had previous experience.

In summary, these studies suggest that the Vivostat applicator has a number of potential clinical advantages over conventional fibrin sealant application systems; it is easy to use, is reproducible and offers a high degree of control. A lower level of blockage than conventional spray systems during intermittent use is a very desirable feature; which allows repetitive applications of small quantities, and is more convenient. Lower airflow and spray forces means that there is less risk of tissue/sealant disturbance and air embolism. The ability to retain a high proportion of the sealant at the target tissue to which it is applied is an important feature of Vivostat application; fibrin sealant wastage is minimised and controlled build up of fibrin sealant layers to the required thickness is possible. Early clinical use of the Vivostat system suggests that surgeons are pleased with the performance of the application system and sealant. Further comparative clinical studies are required to demonstrate that the potential advantages demonstrated for Vivostat in these *in vitro* studies over conventional fibrin sealants are reflected by improved performance in surgical practice.

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