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IF: 5.719**Research Article****Clinical Studies on Performance and Safety of Absorbable Gelatin Sponge - Real World Clinical Experience (RWCE) with Surgispon®**

Vidya Sagar\*, Deepak Patel, Piyush Patel, Anil Kumar, Avni Rana, Bhavin Trivedi

Aegis Lifesciences Pvt. Ltd, Ahmedabad, Gujarat, India – 382213.

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Absorbable Gelatin Sponge (AGS) is a passive haemostat with porous structure, which activates the thrombocytes at the moment blood comes in contact with the matrix of the sponge and causes clotting or Haemostasis. AGS can be effectively used in various surgeries for haemostasis, when control of capillary, venous and arteriolar bleeding by pressure, ligature and other conventional procedures are ineffective or impractical or as adjuvant to surgical procedures. An AGS product, Surgispon® was evaluated for its performance and safety to gain real word clinical experience in relevant surgical procedures of the product. The study was a prospective, single arm, interventional Clinical Registry of 75 surgical procedures with 60 days' clinical follow up. The primary end point was Time To Hemostasis (TTH) and liquefaction

of the sponge at application site. Secondary end point includes handling characteristics of the product during usage and adverse events and serious adverse events on pre and post-operative clinical follow-up. Though patient enrolment was done in 90, clinical follow-up could be done in 75 patients as mandated by study protocol. The handling characteristics of the product during usage on a grading score of maximum 5, was given an average of 4.8. The product performed well with Mean  $\pm$  SD Time To Hemostasis (TTH) of  $3.4 \pm 0.9$  min with liquefaction range of 3 to 5 days in different surgical procedures. The Mean  $\pm$  SD bleeding volume was  $15.5 \pm 2.8$  ml. Surgispon® product handling characteristics were very good and appreciated by all the surgeons. The product meets the study primary and secondary clinical end points. It has not shown any clinical adverse events in 60 days' follow-up. However, no new clinical indications were proposed for Surgispon® in the current Clinical study.

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**Corresponding Author:** Vidya Sagar, Head – Clinical Research, Aegis Lifesciences Pvt. Ltd, Ahmedabad, Gujarat India – 382213.

## INTRODUCTION

Absorbable Gelatin Sponge (AGS), is a sterile, water-insoluble, malleable, gelatin based, absorbable sponge intended for haemostatic use by applying to a bleeding surface. The sponge is off-white and porous in appearance. AGS has porous structure which activates the thrombocytes at the moment blood comes in contact with the matrix of the sponge. This causes the thrombocytes to release a series of substances which promote their aggregation at the same time as their surfaces change character, thus enabling them to act as a catalyst for the formation of the fibrin. AGS can be effectively used in various surgeries for haemostasis, when control of capillary, venous and arteriolar bleeding by pressure, ligature and other conventional procedures is ineffective or impractical or can be used as adjuvant to other modalities in control of bleeding. <sup>[1]</sup> The product becomes liquefied within a week or less and is completely absorbed in three to four weeks, without inducing excessive scar formation and it is highly biocompatible. <sup>[2]</sup>

Hence, AGS is a state of art topical haemostatic agent <sup>[3, 4]</sup> widely used by surgeons in Abdominal Surgery, Anorectal Surgery, Dental Surgery, ENT surgery, Genito Urinary Surgery, Gynaecological Surgery, Hysterectomy, Neuro Surgery, Orthopaedic Surgery, Otolaryngological Surgery, Partial Nephrectomy, Plastic Surgery and Vascular Surgery.

Surgispon® is a well-known international brand of AGS manufactured and marketed by Aegis Lifesciences, India. It is supplied in different models as required for specific clinical applications and in different sizes for surgical procedures as required by physicians and surgeons. It is biocompatible with no tissue reactions in the pre-clinical studies. <sup>[5]</sup> It can be used in combination with thrombin and other drugs as per the surgeon's discretion based on the need. <sup>[6-8]</sup>

The product may be used dry or wet, saturated with isotonic sodium chloride solution. The whole AGS can be used as supplied or cut to the desired size and applied either dry or

saturated saline with light pressure directly to the bleeding site as per physician/surgeon expertise. When applied dry, a single piece of Surgispon® should be manually applied to the bleeding site, and held in place with moderate pressure until haemostasis is achieved.

Aegis Lifesciences was utilizing its own and proven technologies, process and machineries for the manufacturing of AGS. Expert advice from various technocrats, customers, surgeons, research and educational institution, was utilized for the continual improvement and development of the product and processes. Various manuals and published scientific papers on the product are also referred while developing the product. The product is accepted by prominent hospitals/ surgeons around the world.

The product performed extremely well, since last one decade, it's been in market. However, as a post marketing clinical follow-up, the Clinical Registry was under taken further to validate and substantiate the product use in various surgical procedures, indications as real world clinical experience in line with EU MDR 2017/745 regulations. <sup>[9]</sup>

## MATERIALS AND METHODS:

### Study Design:

Prospective, Single Arm, Post Marketing, Interventional study to evaluate Safety and Performance of the Absorbable Gelatine based, Haemostatic Sponge in patients undergoing surgical procedure involving mucosal membrane bleeding, The product is also used in patients undergoing an Abdominal Surgery, Anorectal Surgery, Dental Surgery, ENT surgery, Genito Urinary Surgery, Gynaecological Surgery, Hysterectomy, Neuro Surgery, Orthopaedic Surgery, Otolaryngological Surgery, Partial Nephrectomy, Plastic Surgery, Vascular Surgery.

### Sample Size:

The Surgispon® is an established, marketed product with very satisfactory risk-benefit analysis. Further, the product has neither

changed its composition, technology nor its manufacturing process. The complaints received and the adverse events registered for similar products can be mitigated through training and Instructions For Use (IFU) document. As a result, the statistical sample size for this study is computed to assess any incremental safety issues by way of capturing adverse events and proving or otherwise its efficacy. Further, the statistical sample size was classified to cover various anatomical locations of the body to capture variety of safety and usability concerns, if any, not related to the product but more from the surgeon point of view.

The primary end point is the proportion of the wounds achieving haemostasis within 10 minutes of application of Surgispon®. Setting this proportion as 95%, and then using the statistical sample size determination methods, assuming the permissible margin of error being 10%, and 5% level of significance, the sample size was 128. Assuming that there will 10% patients who will be loss to follow up, we arrive at the sample size of 90 wounds. This sample size is large enough to satisfy the criteria to apply normal approximation to confidence intervals at 95% level.

#### **Study Methodology:**

Investigators and their teams are responsible for the recruitment, enrolment and ethical conduct of the study with manual filling and signature of ICFs. Subjects meeting inclusion and exclusion criteria are invited to participate in clinical follow-up. A screening log of patients declining to participate is maintained. All clinical tests are performed as per the methods provided in the protocol.

All data was collected as manual CRFs. Data management was performed with a third-party vendor or in-house data management team. Interim Data Analysis was performed as and when required. Medical monitoring was performed by trained Clinical Research Professionals of Aegis Lifesciences.

#### **Clinical endpoints:**

The primary end points of the study are the proportion of wounds achieving haemostasis within 10 minutes of application of Surgispon®. Time To Haemostasis (TTH) - Evaluation for haemostasis to begin immediately following application of the Surgispon®. Haemostasis assessments are made every 3 minutes for the first 12 minutes' post application. If haemostasis is not observed within 6 minutes, the treatment site is to be monitored and the research teams to record the specific number of minutes until haemostasis is observed 2. The time taken for liquefaction of the sponge, when placed at the surgical site.

Secondary endpoints include,

1. **Effectiveness:** Device Success (defined as the number of subjects with first bleeding site applications for which haemostasis was obtained within 6 minutes of study device application without the need for adjunctive Treatment).
2. **Haemostatic handling characteristics** (Surgeon's Questionnaire) ease of application to bleeding site as assessed by surgeon questionnaire for haemostatic handling characteristics.
3. **Safety:** Incidence Rate of Device-related Adverse Events and Serious Adverse Events [Time Frame: Procedure, up to 60 days' post procedure].

#### **Clinical Follow – up**

Time frames for the reporting periods for Clinical follow – up are Preoperative, Operative, Day 1, 2, 5, 28 and day 60.

#### **INSTITUTIONAL ETHICS COMMITTEE (IEC), INCLUSION AND EXCLUSION CRITERIA:**

Institutional Ethics Committee or Institution Review Board approval were obtained from the Investigators of respective Hospitals and Institutes, formally after submission of the consent letter and the Clinical Study Protocol (Product Information, Post Marketing Clinical Follow-up (PMCF) Protocol, Informed

Consent Form (ICF), Case Report Form (CRF) etc.).

The study followed ICH standards for Clinical Research including ICH –E6 (GCP) and ICH E3 (Study Reporting); ISO 14155:2011<sup>[10]</sup> and ISO 14971:2019<sup>[11]</sup> standards for Conduct of the study, and applicable local regulatory authorities' standards. The Quality Plan was prepared in accordance with ISO 14155:2011 and ICH-GCP guidelines.

### **Inclusion and Exclusion criteria**

The following inclusion criteria was considered during the study:

1. The subject is 18 years of age or older.
2. The subject is undergoing an Abdominal Surgery, Anorectal Surgery, Dental Surgery, ENT surgery, Genito Urinary Surgery, Gynaecological Surgery, Hysterectomy, Neuro Surgery, Orthopaedic Surgery, Otolaryngological Surgery, Partial Nephrectomy, Plastic Surgery, Vascular Surgery.
3. The subject is willing and able to provide appropriate informed consent.
4. The subject is willing and able to comply with the requirements of the study protocol, including the predefined follow-up evaluations.

Exclusion criteria taken into consideration during the study include:

1. The subject is known or suspected to be pregnant (verified in a manner consistent with institution's standard of care), or is lactating
2. The subject has a known allergy to collagen derived products or any other materials used in the Surgispon® product
3. The subject has an active infection at the surgical site
4. The use of haemostatic agents are contraindicated for the subject
5. The subject has a known bleeding disorder (including thrombocytopenia [ $< 100,000$  platelet count], thrombocytopenia, haemophilia, or von Willebrand disease)

6. The subject has received antibiotic solutions/powders at the intended application site
7. The subject has had surgery at the intended application site  $\leq 6$  months before the current surgical procedure
8. The subject is unavailable for follow-up
9. The subject is currently participating in another investigational device or drug trial.
10. The subject is undergoing ophthalmic or urological procedures.

Of the total study initiated in 90 patients, enrolment and ICF were taken from the all the 90 patients and the study was initiated in May 2020, Clinician expert in the art has explained about the product, benefits and risks and follow up protocols during signing of ICF with the patient. However due to unprecedented Covid - 19 situations, in 15 patients' post-operative follow-up could not be done. In 75 patients, strictly following the Covid protocols as dictated by Indian Government, Indian Council of Medical Research (ICMR) and IEC guidelines, complete follow-up, study could be conducted. All the patients enrolled met the inclusion criteria in the study as described in clinical study protocol.

### **RESULTS AND DISCUSSION:**

#### **Study population: Age, Sex, Medical and Treatment history:**

Study population age was  $45.2 \pm 7.1$  years, with 73 % of males. Four patients had medical history of Diabetes mellitus, Five Patients with hypertension, two patients with Adenomyosis of uterus, two patients with Sinusitis and two patients with Tonsillitis. The enrolled patients are on treatment with Glibenclamide (500mg), Atorvastatin (100mg), Intimacy (2mg), Atrovin, Gentamycin nasal drops, Roxithromycin (250 mg) and erythromycin (500 mg), respectively. All enrolled patients have met the inclusion criteria on preoperative diagnosis. Figure 1 showing the different models and sizes of the product Surgispon® used in the clinical study.

*Fig 1: Images of different models and sizes of the product Surgispon® used in the clinical study.*

In Total, 26.7 % procedures are in Dental Surgery, 20.0 % in Abdominal, 6.7 % in Genito-Urinary, 17.3 % in Orthopaedic

Surgery, 13.3 % in Gynaecological Surgery, 2.7. Neuro Surgery, 13.3 % in ENT Surgery. Data presented in Table 1.

*Table 1: Depicting the types and number of Surgical Procedures in the Clinical Registry*

S. No	Type of Surgical Procedure	No. of Surgical Procedures
1	Dental Surgery	20
2	Abdominal Surgery	15
3	Genito-Urinary Surgery	5
4	Orthopaedic Surgery	13
5	Gynaecological Surgery	10
6	Neuro Surgery	2
7	ENT Surgery	10
	<b>Total Surgeries</b>	<b>75</b>

#### **Operative Data:**

The wound dimensions and bleeding volumes differed based on the surgical site. There were more bleeding volumes in Nasal and Hysterectomy surgeries than the others. The dimensions of the wound are more in Hysterectomy and Orthopaedic and general surgeries. The wound length, width and depth ranged from 10 mm to 2 cm, 4mm to 2cm and 8 mm to 2 mm, respectively. The average bleeding volume was 15.5 ml.

#### **Surgispon® Handling Characteristics**

Effectiveness of handling characteristic was assessed by ease of application to bleeding site, conformance to tissue, ease of preparation for use and delivery to hard-to-reach surfaces. The

handling characteristics of the product during usage on a grading system (1 for Poor to 5 for Excellent scale) was given an average score of 4.8/5.0. All the Surgeons have rated that handling characteristics of Surgispon® as easy and have not found any difficulty in application. Ease of delivery to hard-to-reach surfaces was well appreciated.

#### **Haemostasis and Liquefaction:**

AGS, as packing material and haemostat that does not require removal and has the benefit of being considerably economical compared to other common forms. A comparison was made of the financial cost of several forms of packing for common ontological procedures. In addition, a retrospective audit of complications

was undertaken of all patients in whom the absorbable gelatin sponge was used over the past three years. The absorbable gelatin sponge was shown more economical to use with same efficacy as other similar haemostats and more versatile for use in different surgical procedures. AGS was the choice of haemostatic material for ear packing and surgeries. <sup>[12]</sup>

One of the primary end points of the study, Hemostasis depends on the surgical site and the bleeding volumes etc. Though the product was used in different surgical sites, in 98% of the cases hemostasis was achieved within 3.4 minutes and in other within 7 minutes. With a mean bleeding volume of 15.5 ml hemostasis can be achieved within 3.4 minutes with Surgispon®. TTH without use of adjuvant

treatment was achieved within 10 minutes. Gelatin Sponges have a porous structure which activates the thrombocytes at the moment blood comes in contact with the matrix of the sponge. This causes the thrombocytes to release a series of substances including thromboplastin, which promote their aggregation at the same time as their surfaces change character, thus enabling them to act as a catalyst for the formation of the fibrin. Secondly the sponge has a uniform porosity and reacts naturally to coagulation process. Due to its structure, blood platelets are caught and the coagulation cascade is activated; transforming soluble fibrinogen into a net of insoluble fibrin which stops the bleeding. <sup>[1, 2]</sup> Data presented in Table 2.

*Table 2: Results of the primary and secondary end points in the clinical study*

Description	Mean ± SD (n = 75)
Product handling characteristics	4.8/5.0 (Score)
Bleeding Volumes	15.5 ± 2.8 ml
Time To Hemostasis	3.4 ± 0.9 min
Liquefaction	3.9 ± 0.8 days
AE / SAEs Reported	0

The study met the primary and secondary end points in terms of effectiveness in Hemostasis. In all the cases, Mean liquefaction of the sponge occurred within the range of 3 to 5 days of implantation, except in one case where it happened on 10<sup>th</sup> day. Liquefaction depends on the amount of sponge used, body temperature at the implant site or the mucosal region and the surgical dressing used. It happened in Hysterectomy surgery, as there was more amount of sponge used in the surgery as indicated and adjudicated by the Gynaecologist. In Neuro surgery of Intra spinal procedures only required amount of AGS is used and after hemostasis the excess amount is removed from the surgical site without any complication, up to 60 days' follow-up.

The use of absorbable gelatin sponge for controlling bleeding and preventing adhesions in spinal surgery has the potency of spinal cord compression due to expansion within the

enclosed space, therefore a large piece of absorbable gelatin sponge should be removed once haemostatic control is achieved and small piece, soaked sponge should be used if the sponge is to be left in place, in order to avoid this complication. <sup>[13, 14]</sup> Hence AGS can be used in neuro surgeries by neurosurgeon's skill in this art with adequate preparation and caution. <sup>[15]</sup> However, Gelatin absorbable sponge may mimic a postoperative abscess on Computer Tomography (CT) scan. Findings that may help differentiate the haemostatic agent from abscess include linear arrangement of tightly packed gas bubbles, fixed position of gas bubbles on subsequent examinations, shape, lack of air-fluid level, and lack of enhancing wall. <sup>[16]</sup>

### Adverse Events (AE)/Serious Adverse Events (SAE)

In all the cases of clinical application in different surgical sites, there were no adverse events or severe adverse events reported during the day of operation or surgery and 60 days follow up. Surgispon® was well tolerated, compatible to all the surgical sites in the body and biodegraded without any complications.

### CONCLUSION:

The Clinical study of AGS was conducted in strict adherence to the study protocol and IEC approvals without any study deviations. Due to unprecedented situations of Covid-19, total study population could not be followed-up as per the stipulated time lines. However, with adherence to Covid protocols and IEC guidelines 75 patients enrolled could to me followed up to complete the study and to meet the primary and secondary end points. The study conducted included 4 Hospitals/Institutes and more than seven different surgical sites of implantation. Surgispon® handling characteristics during surgery and implantation were well accepted and appreciated by all surgeons used the product.

Surgispon® has met its primary and secondary clinical end points, in effectiveness of TTH and Liquefaction. No adverse events AE /SAEs were reported in the study with full mandated clinical follow-up of 60 days. In two cases Surgispon® was used in Neurosurgery without any complications. No new risks or new indications of use were identified in the present Clinical Registry.

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