HISTOACRYL® and HISTOACRYL® BLUE TOPICAL SKIN ADHESIVE
Foil Pouch Packaging
Package Insert

Before using product, read the following information thoroughly.

CAUTION: Federal (USA) law restricts this device to sale and use by, or on the order of, a physician.
IMPORTANT! This insert is designed to assist in using Histoacryl® topical skin adhesive. It is not a reference to surgical techniques.

DESCRIPTION:
Histoacryl® and Histoacryl® Blue are sterile, liquid topical skin adhesives composed of n-Butyl-2-Cyanoacrylate monomer. The two products are different in only one respect: Histoacryl® is provided as a colorless liquid, and Histoacryl® Blue is colored with the dye D&C Violet #2 in order to make it easier to see the thickness of the layer of Histoacryl® Blue being applied. Histoacryl® and Histoacryl® Blue topical skin adhesives are supplied in a 0.5 ml single patient use plastic ampoules. Each ampoule is sealed within a foil pouch so the exterior of the ampoule can remain sterile. Histoacryl® remains liquid until exposed to acidic, basic, alcohol, water or water-containing substances, including tissues. Histoacryl® cures (polymerizes exothermically) and forms a film that bonds to the underlying surface. All references to Histoacryl® herein refer to both Histoacryl® (without dye) and Histoacryl® Blue (with dye) unless stated otherwise.

INDICATIONS:
Histoacryl® and Histoacryl® Blue topical skin adhesives are intended for topical application to hold closed easily approximated skin edges of minimum-tension wounds from clean surgical incisions and simple, thoroughly cleansed, trauma-induced lacerations. Histoacryl® and Histoacryl® Blue may be used in conjunction with, but not in place of, dermal sutures.

CONTRAINDICATIONS:
- Histoacryl® topical skin adhesive is not to be applied below the surface of the skin. The liquid adhesive will react exothermically with tissue; the polymerized adhesive is not absorbed by any tissues and may elicit a foreign body reaction.
- Histoacryl® is not to be applied to any internal organs, blood vessels, nerve tissue, mucosal surfaces or mucocutaneous junctions, areas with dense natural hair, or within the conjunctival sac of the eye.
- Histoacryl® is not to be applied to the surface of the eye. If the eyelids are accidentally bonded closed, release eyelashes with warm water by covering with a wet pad. The adhesive will bond to eye protein and will cause periods of weeping which will help to debond the adhesive. Keep the eye covered until debonding is complete – usually within 1 to 3 days. Do not force the eye open.
- Histoacryl® is not to be applied to wounds subject to high skin tension, or on areas of increased skin tension such as the elbows, knees, or knuckles. Histoacryl® is not to be used in areas of skin excision.
- Histoacryl® is not to be applied to wounds that show evidence of infection, gangrene or wounds of decubitus etiology.
- Histoacryl® is not to be used on patients with known preoperative systemic infections, uncontrolled diabetes, or diseases or conditions that are known to interfere with the wound healing process.
- Histoacryl® is not to be used on patients with a known hypersensitivity to cyanoacrylate, formaldehyde, or the dye D&C Violet #2.

WARNINGS:
- Histoacryl® topical skin adhesive should be used only on wounds that have been thoroughly cleaned, debrided and have easily apposed wound edges.
- Histoacryl® generates a small amount of heat during polymerization and should not be applied to tissues that may be affected by such heat.
- Histoacryl® should always be applied very sparingly, either as minute drops or as a very thin film along the edges of the wound. Heavy application may cause thermal damage to tissues, and delayed healing may result.
- Histoacryl® should not be applied to wet wounds. Excess moisture, such as water or alcohol, may accelerate polymerization, resulting in the generation of excess heat.
- Use of Histoacryl® may result in localized sensitization or irritation reactions.
- Application and/or migration (leak) of either version of the product below the surface of the skin will impair the healing process by forming a barrier between tissue edges.
- Histoacryl® Blue migration (leak) below the epidermal surface may result in "tattooing" of the underlying tissue.
- Histoacryl® will readily adhere to most substrates. Care should be taken to avoid unwanted contact with the adhesive during polymerization. Polymerized adhesive can be removed from metal instruments with acetone. Accidental bonding of materials other than tissues may be reversed by peeling apart the adhered surfaces with the aid of warm soapy water, petroleum gel, saline solution, or 5% solution of sodium bicarbonate.
- Accidental bonding of unwanted skin may occur. Do not pull apart skin. Instead, accidental bonding of unintended areas of skin of the body can be corrected with the use of acetone or by soaking in warm water until the skin may be separated.

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PRECAUTIONS:
- Wounds should be kept dry following closure with Histoacryl®. Do not apply topical medications following closure.
- In the event of spillage, Histoacryl® can be absorbed with talc. Flush area with water to solidify the adhesive.
- Histoacryl® has not been evaluated in patients with a history of hypertrophic scarring or keloid information.
- Small quantities of Histoacryl® should be used during wound repair because use of excess Histoacryl® can result in tissue damage due to the cumulative heat dissipated during device polymerization.

ADVERSE REACTIONS:

In studies[1-4] with 1338 patients and 1492 wounds, the following adverse reactions were reported:

Table 1 Adverse Reactions[1-4]

Adverse Reactions	Amiel et al[1]	Barnett et al[2]		Quinn et al[3]		Bruns et al[4]	
	Histoacryl®	Histoacryl®	Sutures	Histoacryl®	Sutures	Histoacryl®	Sutures
N, patients treated	1033	83	80	41	40	30	31
N, wounds treated	1150	100	100	41	40	30	31
*Dehiscence***							
Dehiscence-at Any Time	11 (1.1%)	0/62	0/40	3(8.1%)	2 (5.3%)	1 (3.0%)	1 (3.0%)
Wound Edge Separation Requiring Re-Treatment	1	0	0	2	1	0	0
Infection*							
Suspected Infection	ND	0/62	2/49	1/37 (2.7%)	1/38 (2.6%)	1/30 (3.0%)	ND
Acute Inflammation							
Erythema	57 (5.5%)	ND	ND	1 (2.7%)	4 (11.5%)	ND	ND
Edema	5 (0.5%)	ND	ND	ND	ND	ND	ND
Drainage	20 (1.9%)	ND	ND	ND	ND	ND	ND

ND - No data reported
** Dehiscence was defined as: 1) separation of the incision that required medical attention and that almost exclusively was closed by secondary intention (i.e., Amiel et al[1]) or 2) a wound coming apart by the 7 days follow up visit (i.e., Barnett et al[2]) or a wound requiring delayed primary closure (Quinn et al[3]). A prospective definition for dehiscence was not provided in Bruns et al[4].

*** Infection was defined as: 1) a wound requiring antibiotic treatment (i.e., Amiel et al[1] and Bruns et al[4]) or 2) an area of redness around the wound with or without discharge (i.e., Barnett et al[2]). A prospective definition for wound infection was not provided in Quinn et al[3].

POTENTIAL ADVERSE EFFECTS:
Clinical experience with Histoacryl® used outside the United States suggests that the following adverse events, not reported in the above cited studies, may occur: bonding to unintended tissues, thermal discomfort during polymerization, allergic reaction, foreign body reaction, tattooing, and chronic non-healing of a wound.

CLINICAL STUDIES:
The results of four clinical studies performed with Histoacryl® are summarized below.

1. Amiel et al[1]

A. Study Design

The study was an open-label retrospective trial designed to evaluate the safety and effectiveness of Histoacryl® Blue in approximating surgical incisions at three Israeli centers.

The study population included pediatric patients undergoing elective surgical incisions (i.e., orchidopexy, inguinal hernia, umbilical hernia or hydrocele repair). All incisions were 2 and 5 cm in length, closure was achieved with standard surgical techniques by attending physicians, and final cutaneous closure was performed with Histoacryl®.

Patients were discharged after 4-6 hours of observation. Follow-up visits were 7 days and 4 to 8 weeks (if needed) after surgery. A 12-item questionnaire was completed during a telephone interview with a family member within 6 months after treatment.

B. Study Results

Patient Accounting and Demographics

A summary of patient accounting and demographics as well as wound characteristics is presented in Table 2.

Table 2: Patient Accounting, Demographics, Wound Characteristics
Summary reported by Amiel et. al[1]

Accounting	**No. of pts (%)**
Patient records reviewed	1098
Patients treated with Histoacryl®	1033 (100%)
Wounds treated with Histoacryl®	1150
Patients completing 7 day follow-up	905 (87.6%)
Patients attending 4 week follow-up	401 (38.8%)
Surgical Procedure	**N (%)**
Right inguinal hernia repair	407 (37%)
Left inguinal hernia repair	199 (18%)
Bilateral inguinal hernia repair	119 (11%)
Umbilical hernia repair	43 (4%)
Hydrocele repair	167 (15%)
Orchidopexy	163 (15%)
Patient Age	1 mo – 16 yrs
Wound Characteristics	
Length (cm) range	2 – 5
Depth	ND
Width	ND
Class	ND
Incisions	1150
Lacerations	0
Local Anesthetic use	
Patients using local anesthetic	1033 (100%)

ND - No data reported

C. Study Outcomes

The adverse reactions observed in patients are described in Table 1. 1022/1033 (98.9%) of the patients treated with Histoacryl® achieved wound closure without dehiscence (i.e., separation of the incision that required medical attention).

2. Barnett et al.[2]

A. Study Design

The study was a prospective, randomized trial designed to compare the safety and effectiveness of Histoacryl® Blue and sutures in closing simple pediatric lacerations in an emergency room setting at three facilities in Australia and New Zealand.

Patients between the ages of 4 -12 years were enrolled if they had a clean laceration on any part of the body that was less than 5 cm in length. Patients were excluded if the wound occurred on the eyelid, mucous membrane or a joint margin (i.e. under any added tension) or if the wound required debridement or plastic surgery.

Patients were assessed after wound closure and at 1 week, 3 and 12 months after treatment.

B. Study Results

Patient Accounting and Demographics

A summary of patient accounting and demographics as well as wound characteristics is presented in Table 3.

Table 3: Patient Accounting, Baseline Demographics
and Wound Characteristics Reported in Barnett et al[2]

		Histoacryl® Blue	**Control Sutures**
Patient Accounting			
N. patients enrolled		83	80
N. patients treated		83	80
Patients completed:	1 week	62 (74.6%)	49 (61.2%)
	90 days	46 (55.0%)	44 (55.0%)
	12 months	36 (43.0%)	34 (43.0%)
Patient Demographics			
Mean Age in months (standard deviation)		69.5 (29)	68.4 (30)
Males		48 (57.8%)	68 (85%)
Wound Characteristics			
Length in cm	mean	1.54	1.68
Depth in cm	mean	ND	ND
Width in cm	mean	0.34	0.28
Wound Class: Clean		100 (100%)	100 (100%)
Incisions		0	0
Lacerations		100 (100%)	100 (100%)
Face		49	64
Scalp		35	29
Other		16	7
Use of Anesthesia			
General		0	0
Local only		0	80 (100%)
None		83 (100%)	0

ND – No data reported

C. Study Outcomes

The adverse reactions observed in patients are described in Table 1. Closure of all 200 (100%) wounds was achieved in both treatment groups without dehiscence (i.e., a wound that came apart by the 7 day follow up visit).

3. Quinn et al[3]

A. Study Design

This study was a prospective, randomized controlled trial comparing closure of pediatric facial lacerations with Histoacryl® Blue and sutures in a single Canadian Emergency room facility.

Patients, under the age of 18, with clean facial lacerations less than 4 cm in length and 0.5 cm in width were eligible for enrollment. Patients with wounds requiring deep layer closure, caused by animal bites, lacerations on hair-bearing surface, crossing mucocutaneous junctions or heavily soiled and requiring debridement were excluded from enrollment.

Patients were evaluated immediately after treatment as well as 5 days and 3 months after wound approximation.

B. Study Results

Patient Accounting and Demographics

A summary of patient accounting and demographics as well as wound characteristics are presented in Table 4.

Table 4: Summary of Patient Accounting, Baseline Demographics and Wound Characteristics Reported by Quinn et al[3].

	Histoacryl® Blue	Control Sutures
Patient Accounting		
N, patients enrolled	41	40
N, patients treated	37	38
Patients completed: 90 days	33 (89.1%)	36 (94.7%)
Patient Demographics		
Age (years)	0.7-16	0.5-15
Mean (years)	4.7	4.5
Sex (Male)	58%	42%
Wound Characteristics		
Length in cm mean	1.53	1.52
Depth	ND	ND
Width	ND	ND
Wound Class:	ND	ND
Incisions	0	0
Lacerations (Facial)	37 (100%)	38 (100%)
Use of Anaesthesia		
General	0	0
Local only	0	38 (100%)
None	37(100%)	0

ND – No data reported

C. Study Outcomes

The adverse reactions observed in patients are described in Table 1. Wound closure without dehiscence (i.e., wounds requiring delayed primary closure) was achieved in 34/37 (91.9%) of the Histoacryl® and 36/38 (94.7%) of the suture-treated patients.

4. Bruns et al[4]

A. Study Design

This study was a prospective, randomized trial comparing closure of pediatric lacerations with Histoacryl® Blue and sutures at three emergency rooms within the U.S. All lacerations received routine wound management and lacerations greater than 5 mm in depth were initially repaired with subcutaneous sutures. Patients were then randomized to final cutaneous closure by either Histoacryl® or suture.

Patients between the ages of 1 – 18 years old with lacerations less than 5 cm were enrolled. Wounds requiring the use of subcutaneous sutures were enrolled in this study. Patients with lacerations in areas of high skin mobility or tension (e.g., joints, hands, feet, eyelids, ears, nose, mouth or perineum) were excluded from the study as were lacerations caused by dog bites or extending to the muscle or bone.

Patients were evaluated after wound closure and at 1 week and 2 months after treatment.

B. Study Results

Patient Accounting and Demographics

A summary of patient accounting and demographics as well as wound characteristics is presented in Table 5.

Table 5: Summary of Patient Accounting, Baseline Demographics and Wound Characteristics Reported by Bruns et al[4]

	Histoacryl®	Sutures
Patient Accounting		
N, patients treated	30	31
N, wounds treated	30	31
Attending 2 month visit	30	25
Baseline Demographics		
Median Age	4 years	3 years
Gender (G: male)	24 (80)	25 (80)
Race		
White	14 (47)	19 (61)
Black	16 (53)	12 (39)
Wound Characteristics		
Length in cm median	1.5	1.5
Depth		
< 5 mm	22 (73%)	22 (71%)
> 5 mm	8 (27%)	9 (29%)
Width	ND	ND
Wound Class:	ND	ND
Incisions	0	0
Lacerations (Facial)	37 (100%)	38 (100%)
Local Anesthetic used		
Patients treated with anesthetic	13/30 (43%)	31/31 (100%)

ND – No data reported

C. Study Outcomes

The adverse reactions observed in patients after surgery are described in Table 1. Wound closure without dehiscence (i.e., no prospective definition was provided) was achieved in 29/30 (96.7%) of the Histoacryl® and 30/31 (96.8%) of the suture-treated patients.

HOW SUPPLIED:

Histoacryl® is supplied in 0.5ml single patient use, ampoules. Each ampoule is sealed within a foil pouchl so the exterior of the ampoule can remain sterile. Histoacryl® Blue is supplied in boxes of 10 unit doses. Histoacryl® without the dye, is supplied, in boxes of 10 unit doses.

INSTRUCTIONS FOR USE:

1. Inspect and clean the wound, provide local anesthesia for adequate cleansing and debridement of any devitalized structures, assure hemostasis, close the dermis as needed, and assure that surface edges are easily apposable before applying Histoacryl®.
2. For wounds at risk for tension, before applying Histoacryl® to the skin surface, provide relief of potential stress along the wound line by approximating wound edges with subcuticular sutures.
3. Pull apart or tear the foil pouch to expose the sterile, single patient use ampoule.
4. The ampoule is held at its cannula and rigorously shaken downwards to ensure that no adhesive remains within the cannula. Then the ampoule is opened by twisting off the ribbed tip of the cannula. It is advisable to hold the yellow part of the ampoule between two fingers, holding it vertically with the thin end pointing upward, while opening the ampoule. This will prevent any lost Histoacryl® from escaping from the ampoule when opening.
5. To express Histoacryl® from the ampoule tip, apply light pressure to the ampoule.
6. Appose tissue edges with forceps and hold in apposition while applying Histoacryl® and for approximately 30 seconds after application to allow Histoacryl® to cure and to prevent seepage between wound edges.
7. Apply Histoacryl® to the easily apposed wound edges very sparingly, either as minute drops or as a very thin film along the top edges of the wound. Avoid heavy application.
8. After applying Histoacryl®, maintain light pressure along the wound line to maintain apposition for approximately 30 seconds to allow the adhesive to cure.
9. After Histoacryl® application is completed; discard the ampoule with any remaining adhesive by putting the ribbed tip over the thin end of the cannula, by placing the ampoule in the foil pouch.

PATIENT INSTRUCTIONS (Available in a separate sheet for distribution to the patient):

The following information should be shared with the patient:

- If possible, avoid contact with water for the first 24 hours after treatment and minimize contact with water for an additional 7-10 days. Patients may shower or bathe but allow only transient wetting of the treatment site. The site should not be soaked or exposed to prolonged wetness for 7-10 days or until polymerized film has sloughed off.
- Do not apply any medications or cream to the wound.
- Keep the wound dry with a non-stick, non-medicinal and water resistant bandage, per your doctor's instructions.
- Do not pull or pick at the wound or bandage.
- Avoid extreme physical activity that might dislodge or impact the wound surface.
- Report any discomfort, redness, drainage, swelling or other concerns regarding your wound to your doctor.

STORAGE:

- Histoacryl® always has to be stored in its original sealed foil pouch. Histoacryl® can be stored at ambient conditions (72ºF /22ºC).
- Do not expose Histoacryl® to elevated temperatures (i.e., 104-140ºF, 40-60ºC) for more than eight hours.
- Do not use Histoacryl® after the expiration date shown on the foil pouch, preceded by the expiration symbol.

STERILITY:

Histoacryl® is packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged.

References

1. Amiel GE, Sukhotnik I, Kawar B, and Siplovich L, "Use of N-Butyl-2-cyanoacrylate in Elective Surgical Incisions- Longterm Outcomes," J Am Coll Surg, Vol 189, 21-25 (1999)
2. Barnett P, Jarman FC, Goodge J, Silk G, and Aickin R, "Randomized trial of Histoacryl Blue tissue adhesive glue versus suturing in the repair of pediatric lacerations," J. Paediatr. Child Health 34, 548-550 (1998)
3. Quinn JV, Drezwiecki A, Li MM, Stiell IG, Sutcliffe, Elmsie TJ, and Wood WE, "A Randomized, Controlled Trial Comparing Tissue Adhesive With Suturing in the Repair of Pediatric Facial Lacerations," Annals of Emergency Medicine, 22 (7): 1130-1135 (1993)
4. Bruns TB, Simon HK, McLario DJ, Sullivan KM, Wood RJ, and Anand KJS, "Laceration Repair Using a Tissue Adhesive in a Children's Emergency Department," Pediatrics, 98, 673-675 (1996)

Date of information
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