CASE STUDY

Cyanoacrylates* in Neonatal and Infants Peristomal Skin Damage

ABSTRACT

Introduction: Peristomal skin damage in neonates and infants is an all too common occurrence, and such damage to skin can lead to further complications and morbidity. Given the fragility of the infant or neonatal skin, which is still not fully developed at birth, the clinician's options in terms of choosing a skin protectant are very limited. Denuded skin prevents containment devices from adhering. Skin preps that contain solvents carry associated inhalation and fire hazard risks in a neonatal environment. A relatively new class of materials, cyanoacrylates, is applied solvent-free to the skin, and forms a non-adhesive polymer barrier very quickly. The formation of such film allows relief to the peristomal skin, protects underlying ,skin from further damage caused by leaking gastric mcontents or stoma effluent, and allows the skin to, recover its natural health. It also provides a robust platform for the attachment of a collection device.

Intervention: A cyanoacrylate barrier was applied to infants and neonates with peristomal skin damage in gastrostomy and ostomy patients in an effort to recover denuded skin and, in the case of ostomy patients, increase wear-time of the appliance.

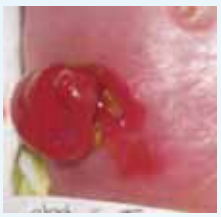
Results: Appliance wear-time was increased for neonatal and infant patients with ostomies. Skin condition improved, and none of the patients developed an adverse reaction to the cyanoacrylate during their stay in the hospital. In previous experience this type of skin breakdown has been difficult to manage.

COMMON MANAGEMENT OF NEONATAL SKIN DAMAGE

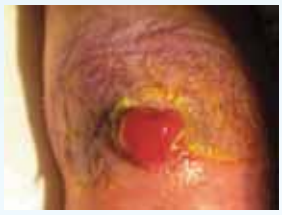
Infants and children have very sensitive skin. In our practice we frequently encounter severe cases of skin breakdown due to a number of issues. Contributing factors include 1) frequent loose stools, 2) leakage of acidic gastric contents from gastrostomy tubes, and 3) harsh enzymatic effluent from an ileostomy. Additionally, denuded skin prevents proper adherence of ostomy pouches requiring frequent pouch changes and additional breakdown of skin. Alternatively a barrier creammay be used over the damaged skin, and the child double-diapered with consequent frequent diaper changes. We have used numerous products in the past to help protect and heal denuded skin with varying degrees of success and have felt that a more robust skin protectant could have a special role in the management of particularly challenging neonatal skin issues.

Case 1

7 week old born at 25 weeks gestation
Stoma opening at skin level 3:00



4-9-2010



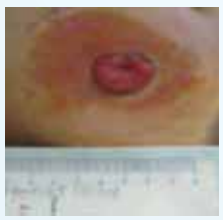
4-13-2010
Skin appears purple and wrinkled from the cyanoacryate application but the disappearance of erythema is clearly visible.

4-15-2010
The erythema and skin breakdown were totally resolved. The cyanoacrylate barrier was applied to the patient on an as needed basis for the following month long stay of the child in the unit.

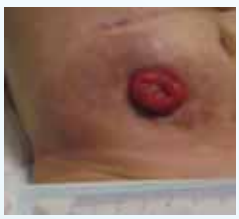
5-10-2010

Case 2

22 month old, 31 week gestation



11-25-2009



11-27-2009

Case 3

17 month old – Necretizing enterocolitis

12-9-2010

The mother of the patient stated that she was unable to keep a pouch on the patient. Cyanoacrylate protectant was applied and the pouch placed around the stoma. The pouch stayed in place 10 hours, and then developed some leaking. At this point the pouch was removed, the skin cleansed with water and dried. Cyanoacrylate protectant was reapplied and patient was double-diapered. Frequent diaper changes were required throughout the night. The skin was seen to be much improved and pink in color in the morning. The cyanoacrylate barrier was intact on the skin and patient was discharged home.

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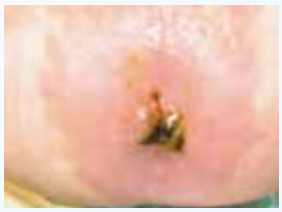
Case 4
14 month old prior gastroschesis patient

1-20-2010

1-21-2010

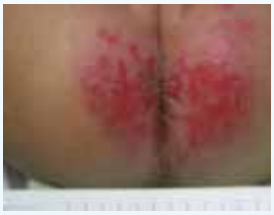
Case 5
Very visible denudement of skin on the buttocks of a child was managed with the application of a cyanoacrylate barrier. The condition of the reddened skin improved and normalcy was restored within a week.

12-6-2010



12-13-2010

Case 6
10 month old baby with influenza



2-14-2011

12-15-2011
"Crusted on" cyanoacrylate barrier, with clearly improved underlying skin with the redness not apparent, within a day of skin management with the cyanoacrylate

TECHNOLOGICALLY ADVANCED MANAGEMENT OF NEONATAL SKIN DAMAGE

Recently we have begun applying a cyanoacrylate skin protectant to cover and protect the skin from further damage from external elements as it heals naturally. We chose for this case series a set of patients whose skin required urgent management due to the severity of the underlying cause and/or the failures of standard methods we had at our disposal for skin protection. The type of cyanoacrylate we used is a non-cytotoxic liquid skin barrier.

OBSERVATIONAL RESULTS

We found that the cyanoacrylate protectant dried within about one minute of application and formed a flexible "crust" over the denuded skin. As the skin regenerated naturally underneath the crust, the product sloughed off in course of time without further intervention. Newer layers of the barrier could be applied to the older partially adherent layers with no ill effects. Once in place and dry, the product allowed for wafers to be placed, in order to allow uninterrupted containment of the sometimes corrosive effluent. We found that use of the cyanoacrylate skin protectant provided the needed protection which allowed our patients' highly denuded skin to resolve in a shorter period of time. We saw no adverse effects from the use of the product in infants or children. During application, we noticed no distress on the patients and the parents reported no concerns about the product use. Based on this, it appears to us that the product likely does not sting on skin that is damaged. The application method via the cracking of unit dose vials was easy and the quantity of product quite sufficient for use on our little patients. The absence of solvents was appreciated by us.

Conclusion: It is remarkable the speed at which the skin issues were resolved after providing robust external protection. It is apparent in these case reports that neonatal skin may regenerate rapidly as long as there is no continuing insult to the already damaged skin from external elements such as corrosive bodily fluids.

* Marathon®, Medline Industries Inc., Mundelein, IL.

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SURGISEAL® Topical Skin Adhesive: A 190 Patient Multi-Center Study

August 2011

BACKGROUND: 2-Octyl Cyanoacrylate has become the topical skin adhesive of choice for most physicians, as evidenced by the growing popularity of the use of these products for surgical wound closure and as a replacement for dermal skin sutures. Adhezion Biomedical's SURGISEAL® is one such 2-octyl cyanoacrylate skin adhesive that has challenged other topical skin adhesives, including the long time market leader, Dermabond® (Ethicon, Inc.) since its U.S. market introduction in early 2010.

TRIAL DESIGN: Five (5) physicians from five (5) separate health care facilities provided prospective data from a total of one hundred ninety (190) patients who underwent twenty-one (21) different procedures utilizing SURGISEAL Topical Skin Adhesive. Data collected was based upon a 45-question patient data collection form completed after each procedure.

RESULTS: 99.5% of the respondents reported an overall positive benefit from the use of SURGISEAL as an adhesive and wound care sealant, while 100% reported better or equivalent cosmetic results compared to sutures. The data also revealed that in 100% of the procedures physicians were able to dispense and apply SURGISEAL adhesive without the applicator clogging.

CONCLUSION: SURGISEAL adhesive performs exceptionally well as a topical skin adhesive compared to surgical sutures and other available skin adhesives.

In early 2010, Adhezion Biomedical, LLC launched its 2-octyl cyanoacrylate SURGISEAL® Topical Skin Adhesive. Unlike other 2-octyl cyanoacrylate skin adhesives, SURGISEAL adhesive is an ultra-pure formulation that is created through a proprietary activation process after complex polymerization, de-polymerization and distillation processes. The result is a solvent- and plasticizer-free solution with exceptional flexibility, strength and the highest Moisture Vapor Transmittance Rate (MVTR) of any surgical cyanoacrylate adhesive available. The product is stored in a sterile, blister pack applicator that will not clog and provides the widest path of microbial protection available.

Between January and June 2011, a multi-center product trial was conducted at five (5) separate health care facilities by five (5) individual surgeons. These physicians had prior experience with Dermabond and other skin adhesives available in the market. Data was collected from 190 surgical cases that represented 21 different procedures.

METHOD

Each physician was provided a three page, forty-five question patient data collection form for use with each surgery. The data collection form included questions relating to, among other items, the surgical procedure, the health of the patient, the surgical incision and the performance of SURGISEAL.

Data was collected post-operatively at one or more of the following intervals: 1-4 days, 5-7 days post op and 25-30 days post op. Physicians completed and signed the patient data collection form prior to returning to Adhezion Biomedical

to be reviewed for completeness and then, data compilation.

PATIENT DATA COLLECTION FORM RESULTS

77.3% of the data forms were collected on day 1-4, while 21.6% were collected on day 5-7 and 1.1% was collected 25-30 days following surgery. 88.9% of the patients were in fine to good health at the time of surgery. 43.1% were male versus 56.8% female. 45.8% were 60 years of age or older, while 54.2% were under 60.

TYPES OF PROCEDURES

Twenty-one different surgical procedures were performed including plastic & reconstructive, orthopedic and gynecological surgeries. These are represented in Table 1.

TABLE 1. Procedure Type & Quantity

Abdominoplasty	10
Liposuction	9
Bilateral Subpectoral Silicone Augmentation	59
Bilateral Subpectoral Saline Augmentation	18
Implant Exchange	3
Mastoplexy	3
Mastoplexy with Subpectoral Silicone Augmentation	6
Bilateral Breast Reduction	6
Bilateral Removal of Axillary Tissue	1
Laparoscopic Hysterectomy	21
Laparoscopic Hysterectomy/LOA/RSO	3
Laparoscopic LAO	10
Laparoscopic RSO	7
Laparoscopic Myomectomy	1
Scar Revision	3
Capsulotomy	1
Total Knee Arthroplasty	18
Total Hip Arthroplasty	6
Gluteus Medius Repair	1
Lateral Unicompartmental Knee Arthroplasty	1
Shoulder Rotator Cuff Repair (3)	3

WOUND CHARACTERISTICS

The location, number, length, depth and width of wounds were recorded and depicted below in Table 2. 42.1% of the wounds were 0-2.0 millimeters, 14.7% were 2.1 – 4.0 millimeters, while 43.1% were greater than 4.0 millimeters. 80.5% had widths of 0 – 3.0 millimeters and 57.9% had incision depths greater than 6.0 millimeters. There were no reports of wound dehiscence and 1 observation (0.5%) of partial dermal breach at day one. Physicians reported that in 96.8% of the cases, approximation time (edges held before releasing) was less than 60 seconds and holding strength expectations were met 97.4% of the time. Finally, in 97.9% of the cases, SURGISEAL was reported to have approximated wound edges adequately and without difficulty.

TABLE 2. Wound Sizes (based on completed data collection forms)

Wound Length	Procedures	Percentage
0mm – 2 mm	80	42.1%
2.1mm – 4.0mm	28	14.7%
>4.0mm	82	43.1%

Wound Width	Procedures	Percentage
0mm – 3.0mm	132	69.5%
3.1mm – 6.0mm	44	23.1%
>6.0mm	14	7.4%

Wound Depth	Procedures	Percentage
0mm – 3.0mm	36	18.9%
3.1mm – 6.0mm	44	23.1%
>6.0mm	110	57.9%

COSMETIC RESULTS AND WOUND HEALING

In 80% of the patient data collection forms, physicians noted that SURGISEAL® adhesive provided a better cosmetic result than sutures. In 20% of the cases, physicians reported that the cosmetic result observation was equivalent to sutures. In 129 or 68% of the cases, physicians indicated that wound healing occurred sooner than expected (as compared to sutures).

FLEXIBILITY

Physicians also compared the flexibility of SURGISEAL to that of other skin adhesives with which they had experience. In 154 surgeries or 81.0% of the time, physicians found SURGISEAL to have "better flexibility" compared to other adhesives. See Figure 1.

EASE OF USE

SURGISEAL adhesive is stored in a foil and Barex blister applicator that can be opened and applied very easily as evidenced by the high rate of positive confirmation observations, i.e. in 97.4% of surgeries, SURGISEAL was reported as "easy to use". See Figure 2.

COVERAGE AND DURATION

In 72.6% of the cases, physicians found that one (1) applicator of SURGISEAL was an adequate volume for the procedure. Since some of these procedures require extraordinarily long incisions, i.e., abdominoplasties, breast augmentation, etc., these results substantiate the excellent coverage of the SURGISEAL 0.35ml applicator. Importantly, physicians also noted that in 129 cases or 67.9% of the time, SURGISEAL was observed to "stay on the wound longer than other adhesives." In 57 surgeries, or 30% of the cases, physicians reported that SURGISEAL was equivalent in product duration. See Figure 3.

DISCUSSION

In this study, SURGISEAL® Topical Skin Adhesive demonstrated favorable results in a variety of plastic and reconstructive, orthopedic and gynecological surgical procedures. As an alternative 2-octyl cyanoacrylate topical skin adhesive to *Dermabond*®, the current market leader, SURGISEAL adhesive provides many important physical properties that substantiate its value in these and other surgical procedures.

Most gratifying in this study, 99.5% of the respondents reported an overall positive benefit from the use of SURGISEAL as an adhesive and wound care sealant, while 100% reported better or equivalent cosmetic results compared to sutures. Finally, on 100% of the data collection forms, physicians noted that they were able to dispense and apply SURGISEAL without the applicator clogging, a well-acknowledged characteristic of other topical adhesive applicators on the market.

FIGURE 1. Flexibility vs. Other Skin Adhesives

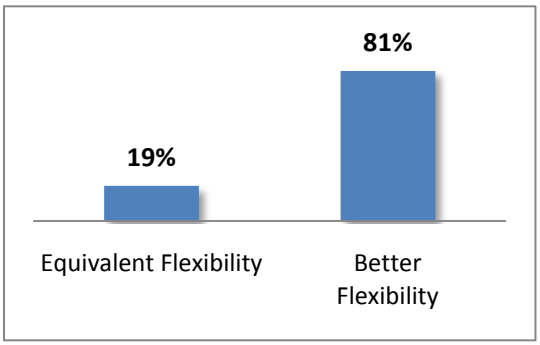


FIGURE 2. Ease of Use in Number of Responses

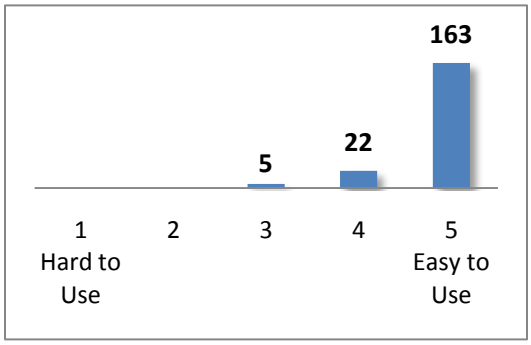
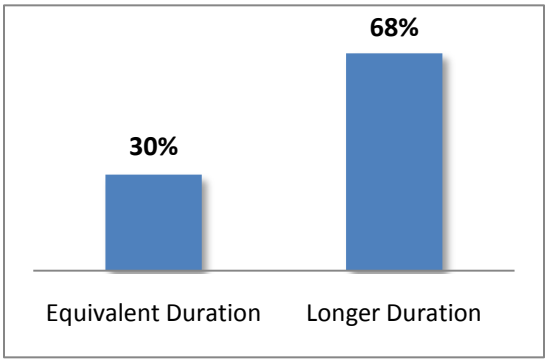


FIGURE 3. Coverage and Duration



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Cyanoacrylate Securement in Neonatal PICC Use

A 4-Year Observational Study

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ABSTRACT

Background: Within every neonatal clinical setting, vascular access devices are considered essential for administration of fluids, nutrition, and medications. However, use of vascular access devices is not without danger of failure. Catheter securement adhesives are being evaluated among adult populations, but to date, studies in neonatal settings are scant.

Purpose: This research describes the prevalence of peripherally inserted central catheter failure related to catheter securement before and after the introduction of tissue adhesive for catheter securement. The identified modifiable risks might be used to evaluate efficacy, to innovate neonatal practice and support future policy developments.

Method and Setting: This was a retrospective observational analysis of routinely collected anonymized intravenous therapy-related data. The study was carried out at the tertiary neonatal intensive care unit (112 beds) of the Women's Wellness and Research Center of Hamad Medical Corporation, Doha, Qatar.

Results: The results showed that the use of an approved medical grade adhesive for catheter securement resulted in significantly less therapy failures, compared with the control group. This remains significant after adjusting for day of insertion, gestational age, birth weight, and catheter type.

Implications for Practice and Research: In parallel with currently published international literature, this study's findings support catheter securement with an octyl-based tissue adhesive in use with central venous catheters. When device stabilization is most pertinent, securement with tissue adhesive is a safe and effective method for long-term vascular access among the neonatal population.

Key Words: catheter securement, CLABSI, complications, cyanoacrylate, infection prevention, neonate

The support and management of neonatal conditions rely upon stable vascular access for supportive therapies (nutrition, transfusion), direct treatment (medications), physiological monitoring (arterial and/or central venous pressure), diagnostic (radiology), and procedural purposes (minimally invasive cardiac interventions).[1,2] However, vascular access device (VAD) use is not without risk, with complications frequently resulting in device failure and significant patient harm. Observational studies have found more than 50% of peripheral VADs[3,4] and 35% of peripherally inserted central catheters (PICCs) in neonates resulted in complications and device failure.[5-9]

Choices in VADs, insertion methods, and management are considered complex and multifaceted, and multiple interdisciplinary clinicians are frequently involved in their care. Evidence-based insertion and maintenance strategies, such as maximum sterile barriers and the use of chlorhexidine gluconate for skin disinfection, are frequently utilized steps to prevent infectious complications[7] and have been developed to reduce the preventable causes of VAD failure and complications, however not always applicable in a neonatal population.[10-15] Dedicated catheter insertion kits and dressing packs for care and maintenance were previously introduced at the facility, along with daily monitoring for device requirement/need, site assessment, and standardized documentation of all related cares and procedures.

Catheter securement issues have serious consequences, and the interaction of patient, practice, and

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All authors contributed to the conceptualization of the study and analysis and interpretation of the data; M.v.R., A.F., and N.A.N. contributed to the design of the initial study and data collection; M.V.R., M.A.M. and N.A.N. drafted the initial manuscript; T.O.O. provided statistical support; M.v.R., K.H., and T.R.S. provided all editorial content review and all revisions to the manuscript; all authors critically reviewed and approved the final manuscript.

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product variables affects securement-related outcomes.[16] Adopting an effective and safe catheter fixation and stabilization method is critical to reducing complication rates. In recent years, international studies and quality improvement initiatives have shown good results in PICC management, fixation, and securement toward reduction of related complications.[17-19] Evidence on catheter securement adhesive in the neonatal population is still scant.

This study aims to describe the prevalence of PICC failure and related complications to catheter securement (eg, phlebitis, infection, accidental removal, catheter damage, and occlusion) before and after the introduction of a tissue adhesive (TA) for catheter securement in the neonatal unit to evaluate efficacy, to identify modifiable risk factors, as well as to inform innovation, practice, and policy development.

DEFINITION

The TA studied (SecurePortIV, Adhezion Biomedical, Wyomissing Pennsylvania) is a medical grade cyanoacrylate, which is the only Food and Drug Administration (FDA)-approved TA for the securement of VADs. Once applied, it has been described to reduce catheter movement, migration, and dislodgement. Additionally, it may help seal the insertion site, keeping the dressing cleaner and dry, potentially reducing unnecessary dressing changes.[17,18] Literature has described some antimicrobial characteristics against micro-organisms usually associated with bloodstream infections related to the use of intravascular catheters.[20] Tissue adhesive for fixation and stabilization of catheters may potentially mitigate the spread of micro-organisms by immobilizing the skin flora at the insertion site and preventing subcutaneous entry.[21]

The FDA has stated that TA may be used safely with both infants and premature neonates, and also with chlorhexidine-sensitive patients. The benefit is that the adhesive can be applied to a very small surface area, in addition to that occupied by the catheter, allowing for fine adjustments of the catheter in any securement position.[22-25] During the time of dressing changes and/or device removal, a silicone-based adhesive remover is used to prevent unwanted medical adhesive-related skin injuries (MARSIs).

What This Study Adds

- Improved securement successes and outcomes from the use of a tissue adhesive.
- Positive impact toward infusion therapy in patients admitted to the NICU.
- Application of medically approved tissue adhesives for vascular device securement in a neonatal population is effective and safe.

METHODS

Design and Setting

This retrospective, observational study utilized routinely collected, anonymized data from January 2017 to December 2020. The main outcome of interest was the occurrence of any complication in relation to PICC use leading to any unplanned removal of the device prior to completion of therapy. The study was performed in a large neonatal intensive care unit (NICU) (112 beds) of the Women's Wellness and Research Centre (WWRC) of Hamad Medical Corporation (HMC), Doha, Qatar.

Ethical Approval

The study design and procedures (MRC-01-20-1053) were approved by the facility's institutional review board (IRB). As the data source was anonymized, the local IRB committee determined the study an "observational chart review" and that participant consent was not required.

Participants and Sample Size

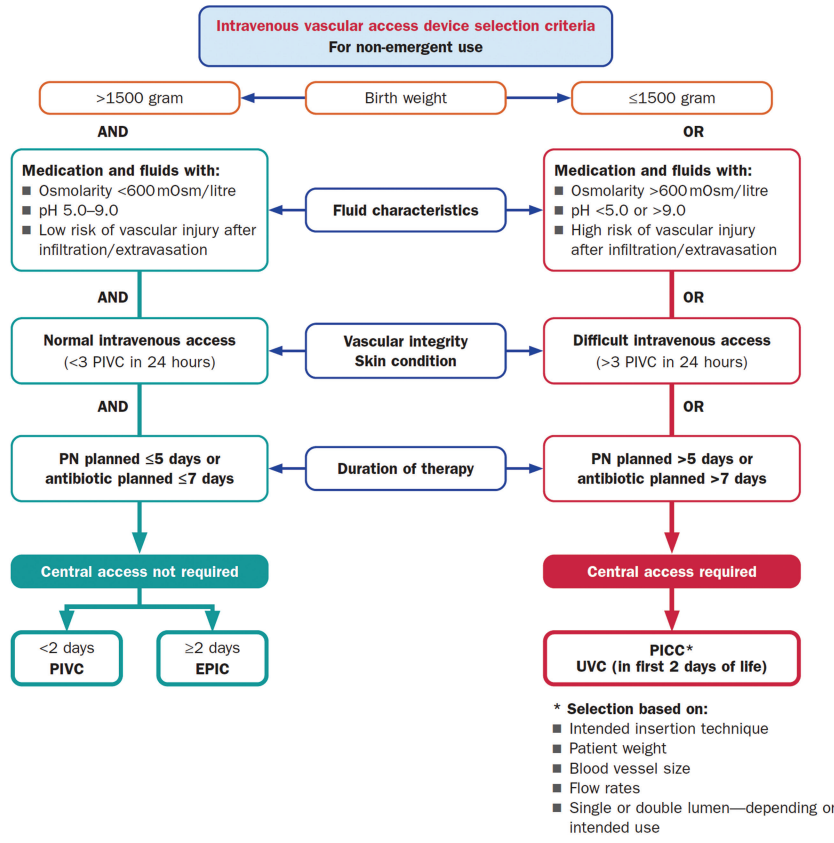
Neonates who were admitted to the NICU and who required intravenous (IV) therapy through a PICC were included in this study. Participants were excluded from the sample if the data collection was incomplete or if it related to the use of other VADs like peripheral IV catheters, and umbilical or surgically placed catheters.

Procedure

In the patient assessment stage, the team follows a locally developed mnemonic, the "5Rs for vascular access" (ie, the Right device, for the Right vein, with the Right therapy, for the Right duration, for the Right patient) as described in a similar concept by Steere et al.[26] PICC cannulation is performed according to the hospital policy, based on current international guidelines and recommendations.[10] Prior to the application of TA, a nonalcoholic, liquid skin barrier is applied to form a protective layer between the epidermis and TA, as well as minimizing irritation from any potentially caustic substances. TA is quick and easy to apply, and documentation of skin irritation or skin damage was noted on removal.

In the study setting, PICC cannulation was routinely performed by physicians and nurses from the neonatal vascular access team (neoVAT). The assessment and selection of appropriate vessels were performed using a near-infrared device (VeinViewer, Christie Medical Inc, Lake Mary, Florida). Vein caliber, length, location of valves, and ability for the vein to fill/empty itself are assessed using a standardized approach. In this practice setting, PICCs are used when infusion therapy is predicted for more

FIGURE 1



EPIC=extended dwell peripheral intravenous catheter; PICC=peripherally inserted central catheter; PIVC=peripheral intravenous catheter; PN=parenteral nutrition; UVC=umbilical venous catheter

Vascular access algorithm/flowchart.

than 5 days. For up to 2 days, short 24 to 26-gauge (Ga) peripheral IV catheters are used, and midlines are inserted when the duration of therapy is expected to last for 5 days (Figure 1). As per Infusion Nurses Society Standards of Practice,[10] antimicrobial-impregnated catheters are recommended if no other measures result in a central line-associated bloodstream infection (CLABSI) reduction and are the preferred choice for all patients weighing less than 1000 g and/or a history of sepsis.[10,17]

Measurements and Data Collection

Patient demographics and baseline data included sex, gestational age at birth (in weeks and days), birth weight (grams), and days of life at insertion. Data regarding procedural demographics included date and time of cannulation, indication for therapy (duration of therapy, difficult vascular access, or fluid characteristics), used type and size of device (1F, 2F, or 3F and whether plain/uncoated or antimicrobial [antibiotic-impregnated] catheters were used), reason for removal (therapy completed and elective removal), catheter-related complications (breakage, leakage), extravasation/infiltration, maintenance-related complications (occlusion, accidental removal), phlebitis, suspected sepsis, patient discharge or transfer (or death), date and time of removal, and the total dwell time in days. Furthermore, the additional key data point included the use of TA for catheter securement.

Data collection is performed by neoVAT members and entered into a dedicated vascular access database. The neoVAT is a nurse-led team, with a dedicated group of 28 nurses and 10 physicians who specialize inserting VADs in the neonatal population and provide a 24/7 vascular access services. Collecting data for this team is essential for several reasons: (1) follow-up on any quality and safety-related issues, (2) overall team and individual clinician performance, (3) monitor cost-effectiveness, (4) provide research and evidence generation, and (5) provide the facility with systemwide benefits of a dedicated vascular access team.

The comprehensive electronic database was developed to collect specific data endpoints linked to the patient demographic, a range of VAD information, peripheral or central placements, including any mechanical, thrombotic, or infectious-related

outcomes. Only neoVAT members have access to the database, which is updated daily and reviewed monthly. Analysis is performed and shared within the NICU and hospital management teams, with individual team members performance shared confidentially. All neoVAT members are responsible for entering and updating the database and a KPI (Key Performance Indicator) is in place to track compliance. It has proven to be an easily accessible option to collect prospective data to improve practices and decrease device failures.

The main outcome was therapy failure defined as any reason for device removal, excluding therapy completed, elective removal, or death from other causes (other than CLABSI). The secondary outcome was the related CLABSI rate within the suspected sepsis group and the use of catheter securement adhesive.

Statistical Analysis

The unit of analysis was each successful PICC insertion. The authors summarized the distribution of data using numbers and percentages, mean and standard deviations, median and interquartile ranges as appropriate. Differences between newborn and insertion characteristics were assessed using the χ^2, *t* test, or Mann-Whitney *U* statistical analysis (Table 1). OpenEpi (Open-Source Epidemiologic Statistics for Public Health, Version 3) was used to compare the incidence rate ratios for suspected sepsis and CLABSI.[27] This was used to compare the incidence rate ratios for suspected sepsis and CLABSI.[27]

Further to this, the authors examined whether there was a statistical significance between TA use versus non-TA use and therapy failure using the Kaplan-Meier test. Finally, a univariable and adjusted Cox-regression analysis was performed to measure the effect of TA use on therapy failure and the incidence rate of CLABSI, reported as hazard ratios (HR) and 95% confidence intervals (CIs). Statistical analysis was performed using SPSS statistical software (IBM SPSS Statistics for Windows, Version 26.0. Armonk, New York)[28] with statistical significance set at $P < .05$.

RESULTS

During the 4-year study period, authors recorded a total of 1842 successful insertions distributed as 449 (24.4%), 431 (23.4%), 432 (23.5%), and 530 (28.8%), for each respective year (2017-2020). A summary of patient characteristics is shown in Table 1. There was no use of TA for catheter securement in 2017 and 2018 while 90.1% of all insertions were secured with TA in 2019 and 2020. Overall, there were 53.1% males and 46.9% females with no

TABLE 1. Demographics of Study Participants[a]

	Tissue Adhesive			
	Total (N = 1842) n (%)	No (n = 975) n (%)	Yes (n = 867) n (%)	*P* Value
Gender				
Male	979 (53.1)	499 (51.2)	480 (55.4)	.072
Female	863 (46.9)	476 (48.8)	387 (44.6)	
Days of life at insertion, median, (IQR)	3 (2-7)	4 (2-8)	3 (2-5)	<.001
GA at birth, mean ± SD	29.6 ± 4	29.4 ± 4.1	29.9 ± 3.9	.008
23-27 wk	577 (31.3)	319 (32.7)	258 (29.8)	<.001
28-31 wk	811 (44.0)	445 (45.6)	366 (42.2)	
32-36 wk	296 (16.1)	118 (12.1)	178 (20.5)	
≥37 wk	158 (8.6)	93 (9.5)	65 (7.5)	
Birth weight, median (IQR), g	1200 (910-1490)	1160 (870-1430)	1290 (965-1540)	<.001
≤999 g	594 (32.2)	356 (36.5)	238 (27.5)	<.001
1000-1499 g	790 (42.9)	429 (44.0)	361 (41.6)	
1500-2499 g	303 (16.4)	107 (11.0)	196 (22.6)	
≥2500 g	155 (8.4)	83 (8.5)	72 (8.3)	
Limb extremity				<.001
Upper	423 (23.0)	285 (29.2)	138 (15.9)	
Lower	1419 (77.0)	690 (70.8)	729 (84.1)	

Abbreviations: GA, gestational age; IQR, interquartile range.
[a]Analysis performed using χ^2, t tests, and Mann-Whitney U tests.

statistically significant difference between the 2 groups. The mean age at birth in the catheter securement TA versus non-TA was 29.9 ± 3.9 versus 29 ± 4.1 weeks, $P = .008$. There were more extreme and very preterm neonates in the non-TA group. Non-TA versus TA for 23 to 27 weeks = 32.7% versus 29.8% and 28 to 31 weeks = 45.6% versus 42.2%, demonstrating a significant difference in the median birth weights of the 2 groups ($P < .001$). Overall, a PICC was inserted at day 3 of life and removed after 11 days, with no significant difference in the duration between both groups.

The most frequently used PICC was the 1F catheter (88.6%) and in general, most PICCs were inserted to facilitate vascular access for a longer duration of therapy (92.6%) (see Table 2). In the TA group, data demonstrated there were more neonates with a birth weight of 1500 g and above. This consequently resulted in more use of 2F PICC (15.9 vs 5.3) in the higher weight group (as per facility policy, insertion of 2Fr PICC is preferred in neonates weighing >1500 g). Over the 4-year period, there was a noticeable shift from using upper extremity veins to lower extremity veins for device placement (see Table 1).

The main reason for device removal was successful completion of therapy (78.0% in the TA group vs 65.3%. in the non-TA group; $P < .001$). Therapy failures due to a complication or death were significantly lower in the TA group (11.7% vs 27.9%, $P < .001$). Main contributing factors to device failure were extravasation/infiltration, device occlusion, phlebitis, suspected sepsis, and death. All device removal details are presented in Table 3.

Stratifying the complications showed no significant rate of therapy failure per gestational age. Suspected sepsis was increased in the 23 to 27 weeks of gestation group and this group was the only patient group where CLABSI was diagnosed (Figure 2).

In the univariate cox regression model, the risk for therapy failure in the TA group was 0.42 times as less likely compared with the non-TA group. This 58% reduction in the risk for failure was still significant after adjusting for days of life at insertion, gestational age (at birth), actual birth weight, and catheter type (either an antimicrobial [antibiotic-impregnated] or conventional plain catheter). The TA group was 0.56 times as less likely to have therapy failure, representing a 44% reduction in risk, compared with the non-TA group adjusted HR 0.56 (95% CI, 0.41-0.79, $P = .001$).

Failure of therapy, resulting in premature removal, occurred in 20.5% of participants (transferred and death excluded), with a complication incidence rate of 13.6 per 1000 device days (total catheter days 25,819, total number complications 350). There was increased number of neonates with suspected sepsis in the non-TA group than in the TA group (see Tables 3 and 4). Likewise for CLABSI with incidence rates of 2.76/1000 days (95% CI, 1.97-3.76) versus 0.99/1000 days (95% CI, 0.53-1.71), there was a demonstrated statistical significance ($P < .001$) in the non-TA versus the TA group.

This study determined a significant reduction in the risk for CLABSI (65%) in the TA group, which was attenuated when adjusted for antimicrobial or nonantimicrobial catheters or other significant newborn characteristics (Table 5).

Regression analysis for type of catheter (antimicrobial/conventional) shows no significant benefit in favor of the antimicrobial catheters related to suspected sepsis and/or CLABSI (see Table 5).

DISCUSSION

The incidence of PICC infusion therapy failure may impact clinical practices, which may negatively

TABLE 2. Reason for Insertion and Type of Catheter Used

	Tissue Adhesive			
	Total (N = 1842) n (%)	No (n = 975) n (%)	Yes (n = 867) n (%)	*P* Value
Reason for insertion				
Duration of therapy	1706 (92.6)	938 (96.2)	768 (88.6)	<.001
Difficult vascular access	86 (4.7)	20 (2.1)	66 (7.6)	
Fluid characteristics[a]	50 (2.7)	17 (1.7)	33 (3.8)	
Catheter type				
1F PICC conventional	914 (49.6)	807 (82.8)	107 (12.3)	<.001
1F PICC antimicrobial[b]	719 (39)	84 (8.6)	635 (73.2)	
2F PICC conventional	182 (9.9)	58 (5.9)	124 (14.3)	
3Fr PICC conventional (surgical placement)	27 (1.5)	26 (2.7)	1 (0.1)	

Abbreviation: PICC, peripherally inserted central catheter.
[a]*pH and osmolarity.*
[b]*Antibiotic-impregnated with rifampicin (antibiotic) and miconazole (antifungal).*

TABLE 3. Reasons for Device Removal, Dwell Time, and Therapy Failure

	Tissue Adhesive			
	Total (N = 1842) n (%)	No (n = 975) n (%)	Yes (n = 867) n (%)	*P* Value
Reason for removal				
1. Therapy completed	1313 (71.3)	637 (65.3)	676 (78.0)	<.001
2. Therapy failure[a]				
Catheter-related complications[b]	43 (2.3)	24 (2.5)	19 (2.2)	
Extravasation/infiltration	50 (2.7)	47 (4.8)	3 (0.3)	
Maintenance-related complications[c]	75 (4.1)	53 (5.4)	22 (2.5)	
Phlebitis	56 (3.0)	42 (4.3)	14 (1.6)	
Suspected sepsis	118 (6.4)	87 (8.9)	31 (3.6)	
Death (CLABSI)	8 (0.4)	6 (0.6)	2 (0.2)	
3. Administrative censoring				
Death (other causes)	44 (2.4)	31 (3.2)	13 (1.5)	
Transferred	135 (7.3)	48 (4.9)	87 (10.0)	
Dwell time, median, (IQR), d	11 (7-16)	11 (7-17)	10 (7-14)	.074
Therapy failure[a]	350 (20.5)	259 (27.9)	91 (11.7)	<.001

Abbreviations: CLABSI, central line-associated bloodstream infection; IQR, interquartile range.

[a]Therapy failure = catheter-related complications, extravasation/infiltration, maintenance-related complications, phlebitis, suspected sepsis, death (CLABSI). Maintenance-related complications are defined as accidental removal and occlusion.

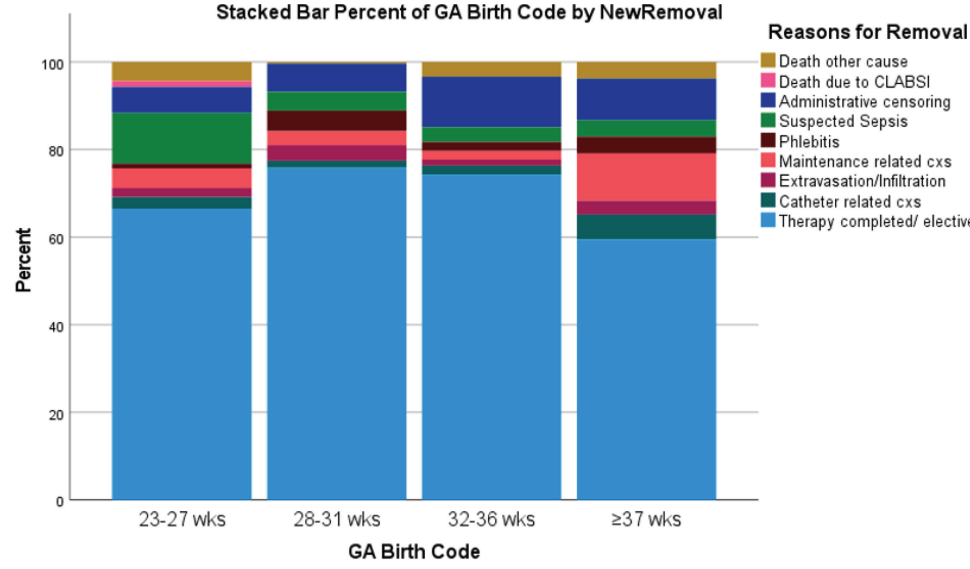
[b]Catheter-related complications are defined as leaking, breakage of the catheter.

[c]Administrative censoring = death (other causes than CLABSI) and neonates transferred out.

affect a neonate's treatment and outcome.[14] The most frequently reported complication was suspected sepsis. The risk for complications was increased in participants with no TA applied for catheter securement. Antimicrobial-impregnated catheters are recommended if no other measures result in a CLABSI reduction.[10,17] In line with a recent study by Gilbert et al,[29] the type of VAD (antimicrobial or conventional) did not affect the risk for CLABSI and therapy failure in this study.

Neonates are an extremely vulnerable patient population. Vascular access devices provide the

FIGURE 2



Bar graph of complications by gestational age.

TABLE 4. Gestational Age and Complications

Reasons for Removal	23-27 wk (n = 577) n (%)	28-31 wk (n = 811) n (%)	32-36 wk (n = 296) n (%)	≥37 wk (n = 158) n (%)	Total (N = 1842) n (%)
Therapy completed[a]	384 (66.6)	615 (75.8)	220 (74.3)	94 (59.5)	1313 (71.3)
Catheter-related complications[b]	15 (2.6)	13 (1.6)	6 (2.0)	9 (5.7)	43 (2.3)
Extravasation/infiltration	12 (2.1)	29 (3.6)	4 (1.4)	5 (3.2)	50 (2.7)
Maintenance-related complications[c]	26 (4.5)	26 (3.2)	6 (2.0)	17 (10.8)	75 (4.1)
Phlebitis	6 (1.0)	38 (4.7)	6 (2.0)	6 (3.8)	56 (3.0)
Suspected sepsis	67 (11.6)	35 (4.3)	10 (3.4)	6 (3.8)	118 (6.4)
Administrative censoring	34 (5.9)	52 (6.4)	34 (11.5)	15 (9.5)	135 (7.3)
Death (due to CLABSI)	8 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.4)
Death (other cause)	25 (4.3)	3 (0.4)	10 (3.4)	6 (3.8)	44 (2.4)
Total	*57 7 (100.0)*	*811 (100.0)*	*296 (100.0)*	*158 (100.0)*	*1842 (100.0)*

Abbreviation: CLABSI, central line-associated bloodstream infection.

[a]Therapy failure (yes) = catheter-related complications, extravasation/infiltration, maintenance-related complications, phlebitis, suspected sepsis, death (CLABSI). Therapy failure (no) = therapy completed and death (other causes than CLABSI).

[b]Catheter-related complications are defined as leaking, breakage of the catheter.

[c]Maintenance-related complications are defined as accidental removal and occlusion.

mainstay of all parenterally administered therapies for these, often-high-risk, patients. Catheter securement is a paramount process in the continuum of vascular device care. While there are several securement options now available to clinicians,[16] there remains a strong push to minimize complications from catheter malposition, often associated with venous thrombosis, vessel perforation, cardiac arrhythmias, cardiac tamponade, pericardial, and pleural effusion.[17]

Cyanoacrylates are high reactivity liquid monomers. When applied to tissue, the monomers flow into the contours of the tissue's surface, providing a strong bond between tissue and glue (via covalent bonds between the cyanoacrylate and functional groups in the tissue proteins).[30] While several TAs have been used in cosmetic surgical procedures (to avoid using skin sutures) for some years, 2-octyl-2-cyanoacrylate is primarily for external use only, as it is able to introduce a serious inflammatory response. Moreover, it is toxic when in contact with noncutaneous tissues.[30]

Recent advances in the study of TAs to provide improved securement of vascular devices have shown promising outcomes across various patient populations. Simonova et al[31] compared 2 different compositions of TA (2-octyl-2-cyanoacrylate and *n*-butyl-2-cyanoacrylate) against 2 polyurethane

TABLE 5. Effects of Catheter Securement on Device Failure and CLABSI

	Tissue Adhesive		*P* Value
	No	Yes	
Effect of catheter securement on therapy failure			
Crude HR	Reference	0.42 (95% CI 0.33-0.54)	<.001
Adjusted HR[a]	Reference	0.61 (95% CI 0.44-0.85)	.003
Adjusted HR[b]	Reference	0.56 (95% CI 0.41-0.79)	.001
Incidence rate (per 1000 catheter days)			
Suspected sepsis	87 (6.01; 95% CI 4.81-7.41)	31 (2.38; 95% CI 1.62-3.38)	<.001
CLABSI	40 (2.76; 95% CI 1.97-3.76)	13 (0.99; 95% CI 0.53-1.71)	<.001
Effect of catheter securement on CLABSI			
Crude HR	Reference	0.35 (95% CI 0.19-0.67)	.001
Adjusted HR[a]	Reference	0.42 (95% CI 0.17-1.06)	.06
Adjusted HR[b]	Reference	0.50 (95% CI 0.19-1.31)	.159

Abbreviations: CI, confidence interval; CLABSI, central line-associated bloodstream infection; HR, hazard ratio.

[a]Adjusted for catheter type only (antimicrobial or nonantimicrobial).

[b]Adjusted for patient characteristics: age from birth (days), gestational age (at birth), actual birth weight, and type of catheter.

(standard and bordered) dressings and an external stabilization device. In this study, device fixation was significantly more effective with *n*-butyl-2-cyanoacrylate over 2-octyl-2-cyanoacrylate.[31]

Strength and physical properties of the cyanoacrylate adhesives are directly related to the structure of the alkyl side chain, and minor changes in the composition may explain the differences in TA strength.[31] Neither TA affected the catheters material, and both required a far greater pullout force than non-fixed controls and current securement dressing methods.[31] Reynolds et al[32] also reported lower arterial catheter failure rates in critical cares settings associated with the use of tissues adhesive.[32]

In a pilot randomized trial, Marsh et al[33] reported catheter failure was lowest in the TA group and highest in the control group (use of standard polyurethan dressing).[33] Four adverse effects (in 3 patients) were observed, all in the TA group (1 skin tear, 2 rashes, and 1 blister); however, these were all minor and resolved with no treatment.[33] Lastly, a large, randomized control trial by Rickard et al[34] reported findings of a 4-arm study comparing several securement methods, with TA demonstrating statistical and clinical significance to prevent device failure.[34] However, the TA composition was *n*-butyl-2-cyanoacrylate, which also reported the highest number of skin adverse events of all 4 groups.[34] The TA composition used in this study was 2-octyl-2-cyanoacrylate, which did not demonstrate any localized skin or MARSI-related injuries.

Barone and Pittiruti[17] describe epicutaneo-caval catheters in neonates may have frequent complications (accidental dislodgement and catheter migration) and often require reassessment of the position of the catheter tip and/or replacement of the catheter in neonates.[17] The authors also reported the frequent use of cyanoacrylate glue for securing different types of venous access devices in their institution, along with the use of a transparent semipermeable dressing and reduced accidental dislodgement from 35% to 20% ($P < .007$; unpublished data).[17] The authors concluded that cyanoacrylate glue is safe, inexpensive and easy to apply, and it yields the additional advantage of being very effective in preventing any bleeding/oozing at the puncture site, adding that removal of cyanoacrylate glue is also consistently easy and harmless.[17]

A recent study also evaluated the clinical efficacy and safety of ultrasound-guided, subcutaneously tunneled, femoral-inserted central catheters in the NICU, securing all devices with TA and a semipermeable transparent dressing.[35] No insertion-related or postinsertion complications were reported, and all patients completed prescribed therapy with one catheter.[35] Recently published clinical guidelines to provide guidance on device selection, device characteristics, and insertion technique for clinicians made no concrete recommendations for securement choices of vascular devices in the pediatric clinical settings.[36] While this appropriateness guide was robust, it was reliant on clinical practice guidelines and consensus of panel members for complex, clinical indications. Unfortunately, no similar neonatal guidelines exist. Therefore, it may not represent other specialized patient populations and should be evaluated accordingly.

Complications after PICC placement may include wound oozing, MARSI, infections, venous thrombosis, mechanical phlebitis, catheter dislodgement, and catheter occlusion. Medical adhesive-related skin injuries are very realistic causes of iatrogenic cutaneous injury and are of importance in all patient populations, frequently predisposing patients to significant infection risk.[37] While TA appears to offer several protective benefits against MARSI, it requires further clinical investigation.

STRENGTH AND LIMITATIONS

To the authors' knowledge, this is the first study of this kind to examine the effect of catheter securement with an approved medical grade cyanoacrylate in the neonatal population in this geographical region. All eligible neonates were included, and the sample size was large and representative of our neonatal PICC population. This increased the statistical power of the study's findings, helping to minimize selection bias and increase the generalizability of the findings to similar settings.

Despite these strengths, there are limitations to this research. This study was a single-center, retrospectively collected dataset, and in contrast to randomized studies, this method creates risk for selection bias. For this study, every infant with a successfully inserted PICC was included to minimize the risk of selection bias. Interrater variability may have affected the results; however, the facility's use of a standardized education program and limiting vascular access procedures to members of a dedicated vascular access team (neoVAT) may possibly have reduced data variability. Data outcomes that were not available for neonates (death not related to CLABSI or were transferred out of the facility) were deemed as administrative censoring (in Table 3). Although this population was small, patients lost to follow-up may have a differing outcome than those who completed the study. Nonetheless, future research should focus on the introduction of new and clinically beneficial strategies to help improve successful therapy outcomes.

CONCLUSION

Several variables demonstrated benefit from the use of a TA for catheter securement, impacting infusion

Summary of Recommendations for Practice and Research

What we know:	• The support and management of neonatal conditions rely upon stable vascular access. • Evidence-based insertion and maintenance strategies have been developed to reduce the preventable causes of vascular access device failure and complications. • Adopting an effective and safe catheter fixation and stabilization method is critical to reducing failure and complication rates. • International studies have shown good results in the use of tissue adhesives for catheter securement. Evidence on catheter securement and tissue adhesive in the neonatal population is still scant and requires ongoing investigation.
What needs to be studied:	• Future research should focus on the introduction of new and clinically beneficial strategies to help improve successful therapy and patient outcomes. • Additional studies are required on the (protective) benefits of tissue adhesive against medical adhesive-related skin injuries. • The use and combination of tissue adhesives with semipermeable transparent dressings and external stabilization devices requires further clinical investigation.
What can we do today:	• Use the "5Rs for vascular access" (ie, the Right device, for the Right vein, with the Right therapy, for the Right duration, for the Right patient). • Aim to optimize catheter securement, fixation, and stabilization of all vascular access devices. • Consider the application of medically approved tissue adhesives for vascular device securement in future practices.

therapies in patients admitted to the NICU. These included reduced risk of extravasation and infiltration, maintenance-related complications (eg, damage caused by sheer and tear forces), phlebitis (mechanical and chemical), suspected sepsis, and death. The risk for the development of a PICC-related complication leading to premature removal of the device increased significantly if no TA for catheter securement was used. The number of events for suspected sepsis and the CLABSI rate were significantly reduced in the TA compared with the non-TA group. In parallel with currently published international literature, this study's findings support catheter securement with an octyl-based TA in use with central venous catheters. When device stabilization is most pertinent, securement with TA is a safe and effective method for long-term vascular access among the neonatal population.

New innovations and clinical advancements in the world of neonatology and vascular device securement, with the least invasive methods, play an important role toward improving patient and device-related outcomes. The use of a medically approved TA for vascular device securement is an important step for clinicians who place and care for VADs in this patient population.

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Section 19: Biocompatibility

As discussed in **Section 14: Device Description** and **Section 15: Substantial Equivalence,** there are no new component materials for the proposed device, SURGISEAL Stylus ™ and Stylus Twist™ Topical Skin Adhesive in comparison to the predicate device, SURGISEAL Topical Skin Adhesive (K082993), with the exception of the application tip.

- The SURGISEAL (Teardrop) has Polyurethane foam with a PE Layer.
- The SURGISEAL Stylus has a Nylon fiber foam tip.
- The SURGISEAL Stylus Twist has a HDPE composition foam tip.

The new proposed devices contain the same base materials as compared to the predicate device. The proposed and predicate devices main active ingredient is a long alkyl chain cyanoacrylate, 2-octyl cyanoacrylate, which is a low-viscosity cyanoacrylate monomer. A trace amount of compatible polymerization accelerator is homogenously mixed with the main ingredient in order to provide a fast dry-time. For visual detection, a small amount of dye, D&C Violet #2, is incorporated into the adhesive formulation.

The difference between the proposed devices SURGISEAL Stylus™ and Stylus Twist ™ Topical Skin Adhesive; and the predicate device's adhesive storage are the following:

- The currently marketed, SURGISEAL™ Topical Skin Adhesive, single-use applicator consists of a thermal formed LDPE/PP/Polyacrylonitrile (Barex 210) foil heated seal on a PET/Aluminum/Polyacrylonitrile backing. This predicate device is supplied at a volume of 0.35mL per applicator.
- The proposed devices SURGISEAL Stylus™ and Stylus Twist ™ Topical Skin Adhesive, single-use applicators consists of an adhesive ampoule contacting Polyacrylonitrile (Barex 210) with an Aluminum ampoule lid including a Polyacrylonitrile inner layer (seal). The applicator sleeve is MDPE. These proposed devices are supplied at a volume of ≥0.50mL per applicator.

The applicator material components of the SURGISEAL Topical Skin Adhesive product family are the same, despite the configurations. Therefore it was determined that it was not necessary to assess the biocompatibility of the material components used to store the adhesive.

The proposed and predicate devices are placed in a secondary package, in order to ensure the sterility level of the device. The material of the secondary package, Tyvek (top layer) and APET (back layer) are the exact same for both the predicate and proposed devices; and therefore it was determined that it was not necessary to assess the biocompatibility of the material components used to maintain the sterile integrity of the device prior to use.

The following table summarizes the biocompatibility testing that was previously conducted to the currently marketed device, SURGISEAL (K082993) per the International Standard ISO-10993, "Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing". The existing testing is deemed supportive of the proposed labeled device, SURGISEAL.

All biocompatibility testing cited in this section was conducted according to Good Laboratory Practice for Non-clinical Laboratory Studies (21 CFR Part 58) by SGS US Testing Laboratories of Fairfield, NJ. Requirements for biological evaluation of the device were based on the International Standard ISO-10993, "Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing".

Table 12: Biocompatibility Test for SURGISEAL (K082993) below presents a summary of the completed biocompatibility tests and corresponding test results.

Table 12: Biocompatibility Test for SURGISEAL (K082993)

Biocompatibility Test	Test Description	Summary of Results	Results
Intracutaneous Reactivity	ISO 10993-10: Test for Irritation and delayed-type hypersensitivity-Intracutaneous (intradermal) reactivity test	No Intracutaneous Hypersensitivity	PASS
Maximization Reactivity	ISO 10993-10: Maximization Test for Delayed Hypersensitivity Test	No Dermal Sensitization Potential	PASS
Systemic Toxicity	ISO 10993-Test for Systemic Toxicity	No Morbidity/Mortality	PASS
Mutagenic Activity: Microbial Reverse Mutation Assay	Ames Assay OECD 471	No Mutagenic Activity	PASS
Local Effects after Muscle Implantation	Tests for Local Effects after Implantation – Short Term implantation in muscle	No Macro or Microscopic Irritation Effects	PASS
Cytotoxicity	ISO 10993-Part 5 – Test for *In-Vitro* Cytotoxicity	Slight Cytotoxic	PASS

Table 13: Biocompatibility Testing of SURGISEAL Stylus™ (SECURESEAL™) and Stylus Twist™ Topical Skin

Biocompatibility Test	Test Description	Summary of Results	Results
Cytotoxicity - (SURGISEAL™ Stylus Topical Skin Adhesive Flock Tip (Lot James A))	ISO 10993-Part 5 – Test for *In-Vitro* Cytotoxicity	No Cytotoxic Effect	PASS
Cytotoxicity – SURGISEAL™ Stylus Twist™ Topical Skin Adhesive (Lot x 5923)	ISO 10993-Part 5 – Test for *In-Vitro* Cytotoxicity	No Cytotoxic Effect	PASS
ISO Intracutaneous Reactivity Test – SecureSeal™ (Lot 121512i)	ISO 10993-10: Test for Irritation and Skin Sensitization	No Dermal Reactions	PASS
Primary Skin Irritation SecureSeal™ - (Lot 121512i)	ISO 10993-10: Test for Irritation and Skin Sensitization	No Dermal Irritations	Pass

The single-use applicator of the currently marketed product, SURGISEAL Topical Skin Adhesive formed by LDPE/PP/Polyacrylonitrile (Barex 210) foil heated seal on a PET/Aluminum/Polyacrylonitrile backing, which houses the adhesive; as well as for the proposed devices, SURGISEAL Stylus™ and Stylus Twist ™ Topical Skin Adhesive, adhesive ampoule contacting Polyacrylonitrile (Barex 210) with an Aluminum ampoule lid including a Polyacrylonitrile inner layer (seal) material are equivalent and therefore the assessment of the adhesive was not repeated. Based on the results from those studies, the proposed and predicate device is considered to be non-toxic, non-mutagenic, non-sensitizing and biocompatible.

Based on the lack of changes conducted to support the requirements for biological evaluation of devices for the exposure (< 24 hours ≥ 30 days), surface-contacting the biocompatibility test method of the currently marketed product is similar, with the exception of the foam.

The SURGISEAL® Topical Skin Adhesive, the currently marketed Polyurethane with a PE Layer foam tip, was assessed per ISO 10993-Part 5 – Test for *In-Vitro* Cytotoxicity and found to be slightly cytotoxic. Further cytotoxic testing of the proposed devices patient-contacting foam, SURGISEAL Stylus Nylon fiber foam tip and the SURGISEAL Stylus Twist has a HDPE composition foam tip were further assessed, the final reports are provided in the following Appendices:

- **Appendix 21: Cytotoxicity test of Stylus Tip**
- **Appendix 22: Cytotoxicity test of Stylus Twist Tip**

In Vitro Cytotoxicity of SURGISEAL STYLUS™ and STYLUS TWIST™ Topical Skin Adhesive

Purpose: The test is designed to determine the biological reactivity of mammalian cell cultures following indirect contact with a test article under test.

Procedure: Testing was conducted in accordance with: Biological Evaluation of Medical Devices-ISO 10993 - Part 5 Test for *In Vitro Cytotoxicity*

Test Article: SURGISEAL Stylus™ Topical Skin Adhesive Flock Tip (Lot James A) and SURGISEAL Stylus Twist™ Topical Skin Adhesive (Lot x 5923)

Test Article Preparation:
A $2cm^2$ sterile disc of filter paper was saturated with test article prior to dosing. One disc per plate was placed on the surface of the agar overlay.

Procedure:
L929 mammalian fibroblast cells, seeded at a density of about 100,000 cells per mL at 7mL per 60 x 15mmplate, were allowed to propagate in serum supplemented minimum essential medium in a single test plate until greater than 80010 confluence was observed. When the cell culture reached confluence, the growth media was removed aseptically and triplicate plates were refilled with serum supplemented culture media containing not more than 2% agar overlay. The flat surface of the test article, positive and negative controls, and media control was then placed in contact with solidified agar surface. The test plates were then returned to the incubator for 24 hours. The plates were individually observed under an

inverted light microscope for signs of cell toxicity. Evaluation of the extent of cytotoxicity, demonstrated as morphological changes in structure, followed the rating guidelines in ISO 10993-5.

Results:

SURGISEAL Stylus™ Topical Skin Adhesive Flock Tip (Lot James A)

Test Article Evaluation of Cytotoxicity	
Lot James A	0,0,0
USP HDPE (Negative Control)	0,0,0
USP Plasticized vinyl containing 10,10'-oxybisphenoxarsine (Positive Control)	4,4,4
Media Control (MEM)	0,0,0

SURGISEAL Stylus Twist ™ Topical Skin Adhesive – Cytotoxicity of Flock Tip (X5923)

Test Article	Evaluation of Cytotoxicity
X5923	0,0,0
USP HDPE (Negative Control)	0,0,0
Black Rubber Stopper (Intermediate Control)	2,2,2
USP Plasticized vinyl containing 10,10'-oxybisphenoxarsine (Positive Control)	4,4,4
Media Control (MEM)	0,0,0

Conclusion:
The test articles (applicator tips) Lot James A and X5923, produced no cytotoxic effects. The controls produced effects consistent for demonstrating assay validity.

Dermal Sensitization Testing of SURGISEAL STYLUS™ Topical Skin Adhesive

In order to confirm that the change of the applicator tips did not elicit dermal irritation potential testing the proposed device, SURGISEAL Stylus patient-contacting foam, Nylon fiber foam tip was evaluated per the an intracutaneous reactivity and primary irritation test in accordance ISO 10993-10: Test for Irritation and Skin Sensitization as seen in the following test reports:

- **Appendix 23: ISO Intracutaneous Reactivity Test**
- **Appendix 24: Primary Skin Irritation**

A.) ISO Intracutaneous Reactivity Test

Purpose: The purpose of this test was to determine if any chemicals that may leach or be extracted from the test article were capable of causing local irritation in the dermal tissues of rabbits.

Procedure: Testing was conducted in accordance with: Biological Evaluation of Medical Devices- ISO 10993-10: Test for Irritation and Skin Sensitization

Test Article: SURGISEAL Stylus™ Topical Skin Adhesive (Lot 121512i)

Test Article Preparation: Each rabbit received five sequential 0.2 mL intracutaneous injections along either side of the dorsal mid-line, with the test article extract on one side and the concurrent vehicle control on the other. The irritation reaction of the test extracts were compared to vehicle controls and recorded over a 72-hour period according to the standard ISO irritation scoring system.

Procedure: The animals were observed daily for abnormal clinical signs. The appearance of each injection site was noted immediately post injection and at 24 ± 2, 48 ± 2 and 72 + 2 hours. The tissue reactions were rated for gross evidence of erythema and edema. The skin was lightly swabbed with dilute alcohol to enhance the appearance of any erythema or edema. The intradermal injection of CSO frequently elicits an inflammatory response. CSO erythema scores < 2 are considered normal. A well-defined positive response is characterized by a score equal to or greater than 2. Table 4 was used to score the reactions.

Table 4: Dermal Observation Scoring

Erythema	Edema
0 = No erythema	0 = No edema
1 = Very slight erythema (barely perceptible)	1 = Very slight edema (barely perceptible)
2 = Well defined erythema	2 = Well defined edema (edges of area well-defined by definite raising)
3 = Moderate to severe erythema	3 = Moderate edema (raised ~1 mm)
4 = Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4 = Severe edema (raised > 1 mm and extending beyond area)

Results: Clinical Observations None of the animals on study showed abnormal clinical signs during the 24, 48, and 72 hour observation periods. Dermal Observations There were no significant dermal reactions observed at the injected test and control sites on the rabbits at the 24, 48, and 72 hour observation periods.

Conclusion: The test was considered valid based upon scientific judgment. The differences in the mean test and control scores of the extract dermal observations were less than 1.0, indicating that the requirements of the ISO Intracutaneous Reactivity Test have been met by the test article.

B.) Primary Skin Irritation

Procedure: This test was designed to determine the dermal irritation potential of the test article on the shaved skin of the rabbit as conducted in accordance with: Biological Evaluation of Medical Devices- ISO 10993-10: Test for Irritation and Skin Sensitization

Test Article: SURGISEAL Stylus™ Topical Skin Adhesive (Lot 121512i)

Test Article Preparation: The Sponsor-supplied test article was dosed neat and negative control patches were applied to the shaved skin of three adult albino rabbits. After a minimum twenty-four hour exposure period, the animals were unwrapped and the negative control patches were removed.

The observations for skin irritation were conducted at 60 ± 6 minutes after unwrapping, and at 24 ± 2, 48 ± 2, and 72 ± 2 hours. A comparative control or control vehicle was run concurrently with the test article. The test was evaluated by an overall collection and interpretation of the data, using the dermal scores as reference marks, and based on the nature and reversibility of the skin lesions.

Procedure: The test article was applied neat as 2.5 cm x 2.5 cm patches directly to the skin and control patches were wet with tap water and applied to the shaved backs of three rabbits (one test article on each side of the vertebral column). Per Sponsor's request, the test article was applied as a uniform layer approximately 2.5 cm x 2.5 cm and allowed to air dry for approximately 30 seconds. A second uniform layer of the test article was applied to the initial 2.5 cm x 2.5 cm application and allowed to air dry for a minimum of 5 minutes. After the minimum 5 minute dry time, the test article was covered with a 2.5 cm x 2.5 cm non-occlusive dressing (such as absorbent gauze), and backed with hypoallergenic tape. The residual test article was left in contact with the skin for the duration of the study (See amendment section). After a twenty-four hour exposure period, the animals were unwrapped and the locations of the patches were marked on the skin to aid in scoring.

Evaluation Criteria

The response of the test article was categorized based on the Primary Irritation Index (PII) shown in Table 2.

Table 2: Primary Irritation Response Categories in the Rabbit

Response Category	Comparative Mean Score (PII)
Negligible	>0 to 0.4
Slight	0.5 to 1.9
Moderate	2 to 4.9
Severe	5 to 8

Note- The Primary Irritation Index (PII) was determined by subtracting the Total Primary Irritation Score for the control sites from the Total Primary Irritation Score of the test sites and dividing that value by the total number of animals used in the study.

Results: Clinical Observations: None of the animals on study showed abnormal clinical signs during the 72 hour test period.

Dermal Observations: There were no significant dermal reactions observed at the test sites on the rabbits at the 60 minute, 24, 48 and 72 hour observation periods.

Calculations: The sum of the erythema and edema scores for the test article and control sites were calculated for only the 24, 48 and 72 hour observation periods for each rabbit. The total scores were divided by 6 (2 observation sites x 3 observation periods) to determine the primary irritation score.

The primary irritation score for the control sites of each rabbit were then totaled and subtracted from the totaled primary irritation score of the test site. This value was then divided by the total number of animals to yield the primary irritation index.

Conclusion: The test was considered valid as the test article remained in contact with skin for a minimum twenty four exposure. Base on the PII for the test article, the irritation response was negligible. Under the conditions of this protocol, the test article is considered a negligible irritant.

OVERALL CONCLUSION:
The results from each of the tests showed that Lot James A and X5923 did not elicit toxicological effects on single or repeated application in vivo. The cytotoxicity evaluation showed a slight cytotoxic score of the predicate device in comparison to the proposed devices. This is considered negligible with no clinical consequences based on all other biocompatibility testing results and the successful clinical use of SURGISEAL.

The results from each of the tests showed that Lot James A and X5923 did not elicit toxicological effects on single or repeated application in vivo. The cytotoxicity evaluation showed a slight cytotoxic score of the predicate device in comparison to the proposed devices. The implantation and irritation study determined that the dermal observations were less than 1.0 which is barely perceptible; as well as being a negligible irritant. This is considered negligible with no clinical consequences based on all other biocompatibility testing results and the successful clinical use of SURGISEAL.

The cytotoxicity tests included a test for mutagenic activity in a bacterial reverse mutagenic assay. Potential mutagenicity was evaluated in the presence and absence of a mammalian liver 8-9 activation system. SURGISEAL, predicate and proposed devices, did not demonstrate mutagenic activity. The irritation and implantation tests assessed the ability for the proposed devices patient contacting material to elicit a potential dermal irritation in an animal model, in order to represent possible clinical affects. The SURGISEAL product families have been found to be biocompatible based on this testing and assessment in accordance with ISO 10993. The results support the commercializing of the SURGISEAL products per its indication for use. Based on the cytotoxic results of the patient-contacting foam for the SURGISEAL products, no further testing was considered necessary.

SurgiSeal Topical Skin Adhesive Used for Clinical Wound Closure

February 2011

BACKGROUND: The cleft lip is a common malformation that affects nearly 1 in 700 newborns worldwide. Repair has been completed utilizing a variety of wound closure devices, including sutures and topical skin adhesives. Evidence suggests repair with a new 2-octyl cyanoacrylate adhesive is an acceptable wound closure method.

STUDY DESIGN: The surgical results of 45 cleft lip repairs and 5 other types of pediatric surgical repairs completed with the use of *SurgiSeal*® topical skin adhesive by 6 pediatric plastic surgeons were reviewed The patients were evaluated at the immediate post-operative period and 4 to7 days after surgery. The patients were evaluated by one pediatric plastic surgeon to assess the resultant scarring, wound leakage, and wound dehiscence.

RESULTS: Physicians reported positive usage and patient results utilizing *SurgiSeal* for the procedures. Key positive feedback was reported in lower rates of cracking or peeling, better flexibility, improved ease of use, better ability to visualize wound healing, and better overall performance than the leading topical skin adhesive in the market.

CONCLUSIONS: Repair of cleft lips with topical skin adhesive as an alternative to sutures has seen positive results in patients, and *SurgiSeal* adhesive performs well in many key clinical attributes.

The cleft lip is a common malformation that affects nearly 1 in 700 newborns worldwide. Clefting of the lip results from a malfusion of the embryological facial elements during the development of a fetus at approximately 6 weeks of gestation.

The resulting cleft lip is repaired when the child is healthy enough to undergo elective surgery. There are many types of repairs used to approximate cleft lips. No cleft lip repair technique has been conclusively shown to give better results than another. Also during cleft lip repair with various techniques, different wound closure methods are utilized by surgeons. These involve different types of suture material as well as skin adhesives.

SurgiSeal is a new skin adhesive developed by Adhezion. This product is FDA approved for use in surgical skin closures. *SurgiSeal* is a 2-octyl cyanoacrylate and provides a water-proof antimicrobial barrier with wound strength properties. The addition of this adhesive to wound closures may improve cosmetic scar results. This study is a review and evaluation of surgical wound closures using *SurgiSeal* skin adhesive in the repair of cleft lip patients.

METHODS

The surgical results of 45 cleft lip repairs and 5 other types of surgical repairs done by 6 pediatric plastic surgeons were reviewed. The patients were selected with the criteria of having a unilateral or bilateral cleft lip repair. There were 5 patients who had did not have a cleft lip repair. These patients had a cranioplasty, lesion removal, or scar revision. The locations of these surgeries were at the Children's Hospital of the King's Daughters in Norfolk, Virginia and at the Operation Smile mission hospital in Guwahati, India. All 50 of the patients had *SurgiSeal* skin adhesive placed onto the wound at the completion of surgery. Each patient had one *SurgiSeal* packet used per wound. The types of sutures used for each incision repair were different and surgeon dependent.

The patients were evaluated at the immediate post-operative period and 4 to7 days after surgery. The patients were evaluated by one pediatric plastic surgeon to assess the resultant scarring, wound

leakage, and wound dehiscence. The *SurgiSeal* questionnaire was answered by the 6 pediatric plastic surgeons taking part in the study.

RESULTS

45 (90%) of the patients who received *SurgiSeal* skin adhesive as a wound closure dressing were primary cleft lip repairs or cleft lip revisions. 2(4%) patients had cranioplasty procedures done, 2(4%) had lesion excisions, and 1(2%) had a scar revision. 37(74%) of the patients were operated on at the Operation Smile mission hospital in Guwahati, India and 13(26%) were done at the Children's Hospital of the King's Daughters in Norfolk, VA and its subsidiary hospitals.

50(100%) of the patients had surgical incisions for which the *SurgiSeal* was used. 50(100%) of patients were evaluated on the day of surgery as well as 4 to 7 days later to assess for inflammation, infection, wound leakage and breakdown.

50(100%) of the patients had surgical sutures used. 50(100%) of the patients had dermal sutures and transcutaneous sutures used. The wording of the questionnaire was confused at this point by several surgeons. All 6 surgeons use both dermal and transcutaneous sutures as opposed to the stated subcuticular and dermal sutures as this terminology was not specific enough.

Approximate wound size table:

Length:

0cm-2cm	15(30%)
2.1cm-4cm	29(58%)
>4cm	6(12%)

Width:

0mm-3mm	50(100%)
3.1mm-6cm	0
>6mm	0

Depth:

0mm-3mm	19(38%)
3.1mm-6cm	29(58%)
>6mm	2(4%)

Post-procedure:

	Yes	No
Improvement in healing	26(52%)	24(48%)
Reduced inflammation	14(28%)	36(72%)
Wound Dehiscence	2(4%)	48(96%)
Wound Infection	1(2%)	49(98%)
Wound leakage	11(22%)	39(78%)

Post-procedure *SurgiSeal* use:

	Yes	No	Not Applicable
Any cracking or peeling of *SurgiSeal* during this procedure	8(16%)	42(84%)	
Any cracking or peeling with *Dermabond*	29(58%)	12(24%)	9(18%)

One of the six surgeons had not used *Dermabond* in the past and could not answer the question regarding cracking and peeling of that product. This surgeon could also not answer question 18-21 due to its comparison opinions of *SurgiSeal* vs *Dermabond*.

Question 17-21: Answers ranked by 6 Pediatric Plastic Surgeons for each of the 50 patients

	1	2	3	4	5	N/A
Cosmetic results of *SurgiSeal* vs sutures alone			1(16.6%)	3(50%)	2(33.3%)	
Flexibility of *SurgiSeal* relative to *Dermabond*				3(50%)	2(33.3%)	1(16.6%)
Ease of use of *SurgiSeal* relative to *Dermabond*			1(16.6%)	1(16.6%)	3(50%)	1(16.6%)
Ability to visualize wound healing of *SurgiSeal* relative to *Dermabond*				1(16.6%)	4(66.6%)	1(16.6%)
Overall performance of *SurgiSeal* relative to *Dermabond*				2(33.3%)	3(50%)	1(16.6%)

(1 being the worst, 3 being equivalent, 5 being the best)

Comparison of *SurgiSeal* to *Dermabond* by 5 Pediatric Plastic Surgeons (Questions 17-21):

17) How did you find the cosmetic results of utilizing *SurgiSeal* vs. sutures alone?

- 5 of 6 surgeons (83.3%) said they find *SurgiSeal* better than sutures (4 or 5)
- 1 surgeon (16.6%) found it equivalent to sutures (3)

18) How would you describe the flexibility of SurgiSeal relative to Dermabond?

- 5 of 5 surgeons (100%) found it more flexible than *Dermabond* (4 or 5)

19) How would you describe the ease of use of *SurgiSeal* relative to *Dermabond*?

- 4 of 5 surgeons (80%) found it easier to use than *Dermabond* (4 or 5)
- 1 of 5 surgeons found it equivalent to *Dermabond* (3)

20) How would you describe the ability to visualize wound healing of *SurgiSeal* relative to *Dermabond*?

- 5 of 5 surgeons (100%) found it easier to see wound healing (4 or 5)

21) How would you describe the overall performance of *SurgiSeal* to *Dermabond*?

- 5 of 5 surgeons (100%) found *SurgiSeal* to be overall better than *Dermabond* in overall performance (4 or 5)

CONCLUSION

There are many products available to close a surgical wound. Most surgeons use various types of sutures to perform this task. Recently there has been an introduction of surgical skin adhesive which has been shown to have favorable results and it is used by many surgeons.

In this study, we were able to have 6 pediatric plastic surgeons use *SurgiSeal* skin adhesive during their cleft lip repair surgeries. 5 of the 6 surgeons in this study have used *Dermabond* in the past. This was the first opportunity for all 6 surgeons to use the *SurgiSeal* skin adhesive product.

The wound types and sizes were very similar for the 50 patients used in this study. All of the wound closures were done on surgical incisions which had dermal and transcutaneous sutures used. All of the surgeons used the product as they would *Dermabond* skin adhesive or as they were instructed as with the surgeon who had not used *Dermabond* in the past.

When reviewing the wounds at 4 to 7 days post surgery the numbers were positive for the *SurgiSeal* use. Improvement in healing was equivocal (52% vs. 48%). Wound infection and wound dehiscence rates were very low, however(3 patients or 6% total). We believe one of the dehiscences occurred in a patient who had wound healing problems that were discovered at the later surgery on the patient's palate. One of the infections and one dehiscence occurred at the surgery site in Guwahati, India. On a previous mission to Guwahati the infection/dehiscence rate for cleft lip repairs was 5.6%. The findings of 2(4%) with *SurgiSeal* use is therefore slightly lower.

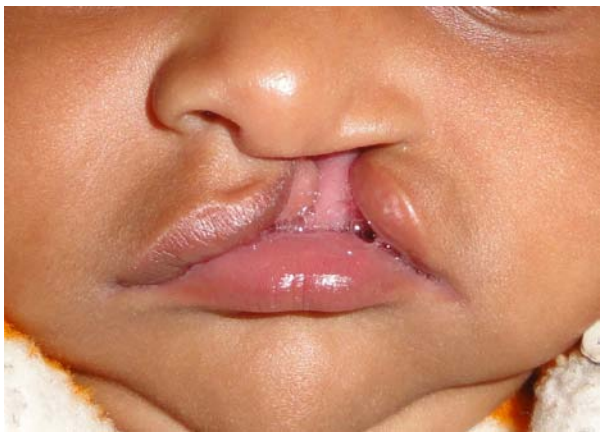
A majority of the surgeons found low rates of cracking or peeling with the *SurgiSeal* product (84%). This is good compared with the 58% of surgeons in this study who experienced cracking or peeling with *Dermabond* in the past. We believe this is mainly due to the flexibility of the product which bends better with the soft tissue movement underneath. The *SurgiSeal* also is applied with more ease so that the material may be placed in a thinner more evenly distributed layer over the tissues.

When reviewing the questionnaire it was easy to see the surgeon's appreciation of the *SurgiSeal* product. 5 of 6(83.3%) surgeons noted they thought the cosmetic result of using *SurgiSeal* was better(4 or 5 on the ranking scale) than sutures alone. 83.3% thought the flexibility of the *SurgiSeal* was better than that of *Dermabond*, and this was shown to be 100% by the surgeons who had used *Dermabond* in the past. 66% of the surgeons found the ease of use to perform better than *Dermabond*. 100% of the surgeons who had used *Dermabond* in the past noted that visualization of the wound was better than with *Dermabond*. Most significantly, 100% of surgeons who had experience with *Dermabond* preferred the performance of *SurgiSeal* to *Dermabond*.

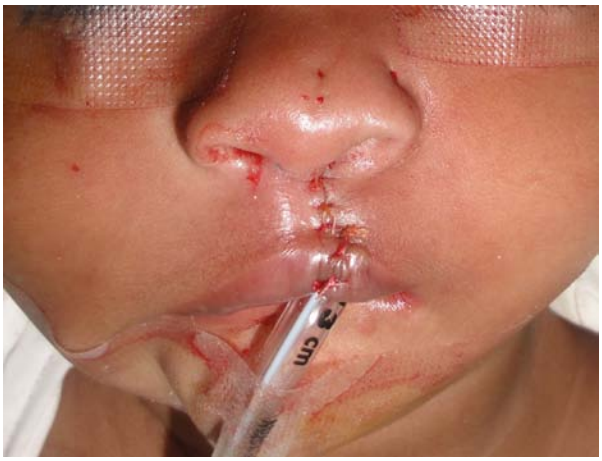
This study was an excellent way to evaluate the use of *SurgiSeal* in pediatric plastic surgery patients. The product held up very well under extreme surgical conditions such as those found in Guwahati, India. The 6 surgeons evaluating the product agreed that they found the use of *SurgiSeal* to be improved over their experience with *Dermabond* especially with its flexibility and visualization properties. All 6 surgeons commented that they would like to use the product in the future. Several ways this study could be improved would be to put *SurgiSeal* and *Dermabond* into a randomized study to evaluate its healing and antimicrobial properties. Also developing a scale to rate the wound appearance cosmetically would lead to a better standardization of results which could be more easily compared to *Dermabond* in competing trials.

Overall, the use of *SurgiSeal* by this group of surgeons had favorable results when used for surgical patients. Additional study to compare its antimicrobial properties and cosmetic advantages would be desired. However, at this time it is easy to see that *SurgiSeal* is an excellent addition to the wound closure product family and a viable skin adhesive that can be used in similar situations in which *Dermabond* had been used in the past.

PRE OP PHOTOS



IMMEDIATE POST OP PRIOR TO PLACEMENT OF SURGISEAL WITH VICRYL SUTURES IN PLACE



4-7 DAYS POST OP