Author's response to reviews

Title: 2-octyl cyanoacrylate versus reintervention for closure of urethrocutaneous fistulae after urethroplasty for hypospadias: a randomized controlled trial.

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Author's response to reviews: see over
Additional files provided with this submission:

Additional file 1: CONSORT checklist.pdf, 646K


Reviewer: Mirko Bertozzi

Reviewer's report:

Major Compulsory Revisions: none

Minor Essential Revisions: none

Discretionary Revisions: The authors could discuss why they choose to close the UCF without fistula edges scarification as suggested by Prestipino et al. and if there was some difference for UCF repair related to the its diameter.

Observations and modifications by the authors (all of them are highlighted in yellow in the main manuscript).

All our patients with UCFs were considered as having late fistulae, as the time between the initial surgical treatment and inclusion in the study was 6 months. Prestipino et al. considered in their article [33] published in 2011 that this duration was the minimum to be considered as defining a late fistula. All children in our study groups were managed with scarification of the edges of the fistulae and all of these were less than 5 mm in diameter.

Prestipino et al. [33] also described those early fistulae or those observed and handled 2 to 3 days after removal of the urinary catheter. The application of the adhesive was direct with no detachment and without scarification or the application of multiple layers. These observations are noted on page 7 lines 159–164. As inclusion criteria, all external orifices of the fistulae were less than 5 mm in diameter (page 6, line 137-138).
Reviewer: MS Ansari

Reviewer's report:

The authors present their experience with 2-Octyl cyanoacrylate in cases of urethrocutaneous fistula. The product has been used previously and has shown results in small-sized fistula. OCA has the advantages like its application on outpatient basis with minimal anesthesia besides its multiple applications.

I wonder the overall fistula rate in the arms is too high i.e. 40% and 32% in OCA and control arm. While, the reported fistula rate in < 5 mm is much less [ref# 7, 25, 26] if done carefully with a 3-layer closure. Similar data with high incidence of failure have been shown by other authors over last one decade. Apparently this may be less expensive the overall surgical cost but the multiple hospital visits and parental anxiety cannot be undermined with every recurrence of fistula.

Many other authors have applied OAC after anatomical closure of fistula and reported much better results.

Observations and modifications by authors (all of them are highlighted in yellow in the main manuscript).

We agree with the observation that careful surgical treatments using multiple layers provide very good results with a low incidence of UCFs compared with simple procedures (page 4, line 103). However, even in recent years, some articles refer to prevalence rates of this complication in excess of 70% (page 10, lines 238 and 240). To support these observations, two new references, numbers 27 and 28 (page 16, line 380 to 383), have been added. We agree with the reviewer that hospital readmissions for new surgery or applications of adhesive represent psychological stress; however, this is less
severe for the outpatient procedure (page 12, line 296 to 297) and the difference in economic costs is significant, as noted on page 9, lines 211–217.

Reviewer: W Farhat

Reviewer's report:

I congratulate the authors for bringing forward a new non-invasive therapeutic method to treat a common post-surgical complication: Urethro-cutaneous fistula after hypospadias repair authors need to define what long-standing UCF?, failed after surgery?

Major revisions:

How did they attach the edges of the orifice? (page 7 line 134): when the treatment was repeated three times did the patients have a foley in situ for 5 days (as mentioned on page 8, line 169). More details need to be added to this section.

Major concern I have about the data and how it is presented is that fistula occurrence is linked to the type of hypospadias and the dynamic nature of the tube created. Hence a tight repair (TIP) may cause a fistula and the correction of the fistula without addressing the distal narrowing may not be sufficient, for that reason I recommend that the authors briefly mention that the fistula repair is only one part of the issue and dealing or addressing the repaired urethra is mandatory. Authors may need to report on the total number of patients treated for hypospadias, describe the type of repair and link to the fistula (total number i.e. with no fistula) and then try to see if the treatment option is more successful when the narrowing was ruled out or type of repair. By presenting the data as suggested, the value of the work will be more diverse and helpful to guide the surgeons in their decision and more importantly, the success rate of the treatment offered may be also higher.
A statistician needs to look at the sample size, the power and the complication rate is not very accurate and thus the number of patients recruited is not clear.

What do the authors mean by congenital malformations on page 10, line 206.

**Observations and modifications by the authors (all are highlighted in yellow in the main manuscript).**

Congenital malformations are described in Table 1, as stated on page 8, line 199. The orifice edges were attached with Adson forceps and technique details are described on page 7, lines 159–163.

As shown in Figure 1, 55 patients were assessed for eligibility but 13 of them did not provide consent. Most of these patients were referred from other hospitals located in five Mexican states of the western part of the country. Only five patients were treated primarily from the hospital where this clinical trial was conducted, out of 115 patients who underwent surgery primarily in our institution during the study period. We are unable to provide the total number of patients treated during the 6-year study period in all referral hospitals of the Mexican Institute of Social Security.

As described on page 5, lines 117–121, the purpose of the study was to evaluate the effectiveness of 2-octyl cyanoacrylate adhesive in treating UCF and to avoid reoperations. The objective of our study was not to establish any differences in the incidence of complications between surgical techniques employed to treat primary hypospadias according to its location.

We determined the sample size taking into account the 25% prevalence of UCF after primary surgical treatment and 75% for the persistence of UCF after medical treatment (a spontaneous closure rate of 15–30% has been reported particularly in fistulae with
less than 2 mm of orifice diameter) as described on page 6, lines 132–136. We did not consider consulting a statistician to define the sample size.

In support of this point, the success rate with surgical treatment was slightly higher in the surgical group (68% versus 60% with OCA, P = 0.58), but these patients required 3.5 ± 1.2 surgical reinterventions to obtain closure.

We conclude that this medical treatment with an adhesive is a good option to treat UCF as an alternative to surgical reinterventions. As stated by Hosseini et al. (page 11, lines 267–276, reference 35), we propose the use of adhesive as a dressing for the suture line after surgical repair of UCF to prevent complications such as haematomas and infections, which precipitate dehiscence and UCF.