

# THE EFFECT OF TOPICAL GENTAMYCIN APPLICATION AT THE URETHRAL STENT TO THE URETHRAL STENT'S BACTERIAL COLONY-FORMING-UNIT COUNTS IN HYPOSPADIAS PATIENTS PERFORMED URETHROPLASTY

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## ABSTRACT

**Objective:** To determine the effect of topical gentamycin application at the urethral stent to the stent's colony-forming-unit (CFU) in hypospadias patients. **Material & methods:** This study is a double blind prospective randomized controlled study, conducted from November 2016 - August 2017 in Urology Department Hasan Sadikin Hospital Bandung. We include patients with distal until penoscrotal hypospadias who underwent urethroplasty for the first time. The subjects were divided into 2 groups: Group A were patients performed urethroplasty with nasogastric tube (NGT) urethral stents only. Group B were patients performed urethroplasty with NGT urethral stents that were coated with topical gentamycin. Both group were operated by a single surgeon using either Tubularized Incised Plate (TIP) or Onlay Preputial Flap technique. Both group used supra pubic urinary diversion. Both group were given the same preoperative and postoperative intravenous antibiotics and given same dressing. At post operative day 7, the stents were removed and swabbed for bacterial culture and resistance test and colony-forming-unit (CFU) counts. Demographic data is described and, among others were analyzed statistically. Other adverse events and complications were also documented. **Results:** There were 25 hypospadias patients who were performed urethroplasty (12 patients in Group A and 13 patients in Group B). The median age in group A was  $7 \pm 2.995$  (years old) and the mean age in group B was  $6 \pm 3.178$  (years old). In group A, 1 patient (8.3%) were distal shaft type, 1 patient (8.3%) were middle shaft type, 8 patients (66.7%) were penoscrotal type, 1 patient (8.3%) were proximal shaft type, and 1 patient (8.3%) were subcoronal type. In group B, 3 patients (23.1%) were distal shaft type, 3 patients (23.1%) were middle shaft type, 5 patients (38.5%) were penoscrotal type, and 2 patients (15.7%) were proximal shaft type. In group A, 6 patients (50%) using TIP, 6 patients (50%) using onlay preputial flap. In group B, 5 patients (38.5%) using TIP, 8 patients (61.5%) using onlay preputial flap. In Group A, *Staphylococcus haemolyticus* was the most common bacterial found in urethral stent swabbed culture (50%), followed by *Pseudomonas aeruginosa* (16.7%), *Acinetobacter baumannii* (8.3%), *Enterococcus faecalis* (8.3%), *Morganella morganii* (8.3%) and sterile cultures (8.3%). In Group B, 38.5% were sterile urethral stents culture, followed by *Staphylococcus haemolyticus* (30.8%), *Enterobacter cloacae* (7.7%), *Staphylococcus warneri* (7.7%), *Staphylococcus epidermidis* (7.7%), and *Moraxella catarrhalis* (7.7%). The most sensitive antibiotics in both group were Amikacin, Gentamycin, Meropenem, Cotrimoxazole, and Cefepime. In group A, 11 patients (91.7%) had  $>100.000$  CFU counts, and 1 patient (8.3%) with no colony found. In Group B, 2 patients (15.4 %) had  $>100.000$  CFU counts, 6 patients (46.2%) had  $<100.000$  CFU counts, and 5 patient (38.5%) with no colony found. In group A, there were 3 patients (25%) with urethra-cutaneous fistula, 4 patients (33.3%) with hematoma, and 5 patients (38.5%) without any complications. In group B, there were 2 patients (15.4%) with urethra-cutaneous fistula, 3 patients (23.1%) with hematoma and 8 patients (61.5%) without any complication. Using Mann-Whitney U-test, we found a significant difference of CFU counts formation between the two groups ( $p=0.001$ ). Statistically, the lesser CFU counts found, the lesser complication were developed ( $p=0.001$ ). **Conclusion:** Topical gentamycin application at the urethral stents in hypospadias patients performed urethroplasty significantly reduced CFU counts found at the urethral stents and thus reduced the urethra-cutaneous fistula and hematoma formation.

**Keywords:** Topical gentamycin, urethral stent, colony-forming-unit, hypospadias, urethroplasty.

## ABSTRAK

**Tujuan:** Menentukan pengaruh pelapisan stent uretra dengan Gentamycin zalf terhadap jumlah koloni kuman yang ditemukan pada stent uretra pasien hipospadia yang dilakukan uretroplasti. **Bahan & Cara:** Penelitian ini adalah penelitian prospektif randomized controlled study (RCT) dari November 2016 - Agustus 2017 di Departemen Urologi RSUP Hasan Sadikin Bandung. Kriteria inklusi adalah pasien hipospadia tipe distal sampai dengan penoskrotal yang dilakukan uretroplasti untuk pertama kalinya. Subyek secara acak dibagi menjadi 2 kelompok, kelompok A adalah kelompok kontrol, dimana stent nasogastrik tidak dilapisi oleh salep gentamycin. Kelompok B adalah kelompok perlakuan, dimana stent

nasogastrik dilapisi oleh salep gentamycin. Kedua kelompok dioperasi oleh satu operator menggunakan teknik Tubularized Incised Plate (TIP) or Onlay Preputial Flap technique. Kedua kelompok menggunakan sistostomi sebagai diverti urin. Kedua kelompok diberikan antibiotik preopratif dan pasca operasi serta balutan yang sama. Stent uretra dicabut pada hari ke-7 setelah operasi dan dilakukan pemeriksaan kultur, resistensi, dan jumlah koloni kuman stent NGT. Data karakteristik, hasil penelitian dan komplikasi operasi dikumpulkan dan dianalisa secara statistik. **Hasil:** Terdapat 25 pasien hipospadia yang dilakukan uretroplasti (12 pasien kelompok A, 13 pasien kelompok B). Median usia kelompok A adalah  $7 \pm 2.995$  tahun dan median usia kelompok B adalah  $6 \pm 3.178$  tahun. Pada kelompok A, 1 pasien (8.3%) tipe distal shaft, 1 pasien (8.3%) tipe middle shaft, 8 pasien (66.7%) tipe penoscrotal, 1 pasien (8.3%) tipe proximal shaft, dan 1 pasien (8.3%) tipe subcoronal. Pada kelompok B, 3 pasien (23.1%) distal shaft, 3 pasien (23.1%) tipe middle shaft, 5 pasien (38.5%) tipe penoscrotal, dan 2 pasien (15.7%) tipe proximal shaft. Pada kelompok A, 6 pasien (50%) menggunakan TIP, 6 pasien (50%) menggunakan onlay preputial flap. Pada kelompok B, 5 pasien (38.5%) menggunakan TIP, 8 pasien (61.5%) menggunakan onlay preputial flap. Pada kelompok A, *Staphylococcus haemolyticus* adalah kuman yang paling banyak ditemukan pada kultur stent NGT (50%), diikuti oleh *Pseudomonas aeruginosa* (16.7%), *Acinetobacter baumannii* (8.3%), *Enterococcus faecalis* (8.3%), *Morganella morganii* (8.3%) dan steril (8.3%). Pada kelompok B, 38.5% steril, diikuti oleh *Staphylococcus haemolyticus* (30.8%), *Enterobacter cloacae* (7.7%), *Staphylococcus warneri* (7.7%), *Staphylococcus epidermidis* (7.7%), dan *Moraxella catarrhalis* (7.7%). Antibiotik yang paling sensitif pada kedua grup adalah Amikacin, Gentamycin, Meropenem, Cotrimoxazole, and Cefepime. Pada kelompok A 11 pasien (91.7%) memiliki jumlah koloni kuman  $>100.000$  CFU, dan 1 pasien (8.3%) tidak ditemukan kuman. Pada kelompok B, 2 pasien (15.4%) memiliki jumlah kuman  $>100.000$  CFU, 6 pasien (46.2%) memiliki jumlah kuman  $<100.000$  CFU, dan 5 pasien (38.5%) tidak ditemukan koloni kuman. Pada kelompok A 3 pasien (25%) terdapat fistula uretrokutan, 4 pasien (33.3%) terdapat hematom, dan 5 pasien (38.5%) tidak terdapat komplikasi. Pada kelompok B, terdapat 2 pasien (15.4%) dengan fistula uretrokutan, 3 pasien (23.1%) dengan hematom dan 8 pasien (61.5%) tanpa komplikasi. Pada uji Mann-Whitney U-test, terdapat perbedaan bermakna jumlah koloni kuman pada kedua kelompok ( $p=0.001$ ). Secara statistik, semakin sedikit jumlah koloni kuman, semakin sedikit komplikasi yang dapat timbul ( $p=0.001$ ). **Simpulan:** Pelapisan stent uretra dengan Gentamycin zalf mengurangi secara signifikan jumlah koloni kuman yang ditemukan pada stent uretra pasien hipospadia yang dilakukan uretroplasti sekaligus mengurangi komplikasi fistula uretrokutan dan hematom.

**Kata kunci:** Gentamycin topikal, stent uretra, jumlah koloni kuman, hipospadia, uretroplasti.

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## INTRODUCTION

Hypospadias is a birth defect in boys characterized by the meatus is not in placed at the Tubularized Incised Plate (TIP) of the glans penis. Hypospadias is a common condition, with an incidence of 3.2 per 1000 live births. The treatment is only surgical and there is no universal operative technique.<sup>1</sup>

Infection is the most common complication of urethroplasty despite preoperative and post-operative antibiotics given.<sup>2</sup> Infection may lead to other serious complications such as urethra-cutaneous fistula formation.<sup>3</sup>

Urinary diversion or urethral stenting is usually needed to prevent urethra-cutaneous fistula formation and urethral stenosis. Urethral stents may lead to bacterial colonization similarly to all inserted synthetic medical devices.<sup>4</sup>

According to Arsyad et al, one of the simplest method to prevent infection due to stenting is to apply topical antibiotics to the stent's surface.<sup>5</sup> It was proven that topical antibiotics might adhere to

stent's surface at the bactericidal level and slow bacterial adherence to the stent's surface.<sup>6</sup>

Topical gentamycin is a wide spectrum antibiotics that is bactericidal to both gram-positive and negative bacteria usually used for bacterial conjunctivitis.<sup>7</sup>

Study about topical gentamycin to prevent infection after urethroplasty in hipospadia is still limited. In this study we evaluate the effect of topical gentamycin to the urethral stent bacterial colonization.

## OBJECTIVE

To determine the effect of topical gentamycin application at the urethral stent to the stent's colony-forming-unit (CFU) in hipospadias patients.

## MATERIAL & METHODS

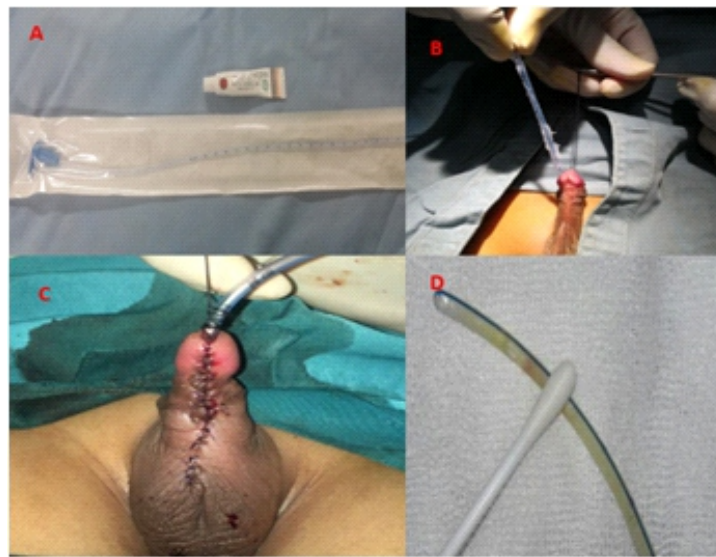
This study is a double blind prospective randomized controlled study, conducted from November 2016 - August 2017 in Urology

Department in Hasan Sadikin Hospital. We include patients with distal until penoscrotal hypospadias who underwent urethroplasty for the first time.

The subjects are divided into 2 groups: Group A are patients performed urethroplasty with nasogastric tube (NGT) urethral stents only. Group B are patients performed urethroplasty with NGT urethral stents that were coated with topical gentamycin. Both group are operated by a single surgeon using either Tubularized Incised Plate (TIP)

or Onlay Preputial Flap technique. Both group are using supra pubic urinary diversion. Both group are given the same preoperative and postoperative intravenous antibiotics and given same dressing.

At post operative day 7, the stents are removed and swabbed for bacterial culture and resistance test and colony-forming-unit (CFU) counts. Demographic data is described and, among others were analyzed statistically. Other adverse events and complications were also documented.



**Figure 1.** A. Application gentamycin zalf to NGT stent, B. Insertion of NGT stent to neo-urethra, C. Urethroplasty, D. NGT stent swabbed at POD 7.



**Figure 2.** A. Clinical appearance of neo-urethra of sterile NGT stent, B. Infected NGT stent.



## RESULTS

There were 25 hypospadias patients who were performed urethroplasty (12 patients in Group A and 13 patients in Group B). The median age in group A was  $7 \pm 2.995$  years old and the mean age in group B was  $6 \pm 3.178$  years old (Table 1).

In group A, 1 patient (8.3%) were distal shaft type, 1 patient (8.3%) were middle shaft type, 8 patients (66.7%) were penoscrotal type, 1 patient (8.3%) were proximal shaft type, and 1 patient (8.3%) were subcoronal type. In group B, 3 patients (23.1%) were distal shaft type, 3 patients (23.1%) were middle shaft type, 5 patients (38.5%) were penoscrotal type, and 2 patients (15.7%) were proximal shaft type (Table 1).

In group A, 6 patients (50%) using TIP, 6 patients (50%) using onlay preputial flap. In group B, 5 patients (38.5%) using TIP, 8 patients (61.5%) using Onlay Preputial Flap (Table 1).

In Group A, *Staphylococcus haemolyticus* was the most common bacterial found in urethral stent swabbed culture (50%), followed by *Pseudomonas aeruginosa* (16.7%), *Acinetobacter*

*baumannii* (8.3%), *Enterococcus faecalis* (8.3%), *Morganella morganii* (8.3%) and sterile cultures (8.3%). In Group B, 38.5% were sterile urethral stents culture, followed by *Staphylococcus haemolyticus* (30.8%), *Enterobacter cloacae* (7.7%), *Staphylococcus warneri* (7.7%), *Staphylococcus epidermidis* (7.7%), and *Moraxella catarrhalis* (7.7%) (Table 2).

The most sensitive antibiotics in both group were Amikacin, Gentamycin, Meropenem, Cotrimoxazole, and Cefepime (Table 3).

In group A, 11 patients (91.7%) had  $>100.000$  CFU counts, and 1 patient (8.3%) with no colony found. In Group B, 2 patients (15.4 %) had  $>100.000$  CFU counts, 6 patients (46.2%) had  $<100.000$  CFU counts, and 5 patients (38.5%) with no colony found (Table 4).

In group A, there were 3 patients (25%) with urethra-cutaneous fistula, 4 patients (33.3%) with hematoma, and 5 patients (38.5%) without any complications. In group B, there were 2 patients (15.4%) with urethra-cutaneous fistula, 3 patients (23.1%) with hematoma and 8 patients (61.5%) without any complication (Table 5).

**Table 1.** Characteristic of general population.

| Total Population (N = 25) | Group A ( N = 12 )        | Group B ( N = 13 )        |
|---------------------------|---------------------------|---------------------------|
| Median age                | $7 \pm 2.995$ (years old) | $6 \pm 3.178$ (years old) |
| Type of hypospadias       |                           |                           |
| Distal                    | 1 (8.3%)                  | 3 (23.1%)                 |
| Midshaft                  | 1 (8.3%)                  | 3 (23.1%)                 |
| Proximal shaft            | 1 (8.3%)                  | 2 (15.4%)                 |
| Subcoronal                | 1 (8.3%)                  | 0 (0 %)                   |
| Penoscrotal               | 8 (66.7%)                 | 5 (38.5%)                 |
| Operation technique       |                           |                           |
| Tubularized incised plate | 6 (50%)                   | 8 (61.5%)                 |
| Onlay preputial flap      | 6 (50%)                   | 5 (38.5%)                 |

**Table 2.** Distribution of bacteria found at the NGT stent culture.

| Bacteria                           | Group A<br>Frequency | Bacteria                           | Group B<br>Frequency |
|------------------------------------|----------------------|------------------------------------|----------------------|
| <i>Acinetobacter baumannii</i>     | 1 (8.3%)             | <i>Enterobacter cloacae</i>        | 1 (7.7%)             |
| <i>Enterococcus faecalis</i>       | 1 (8.3%)             | <i>Moraxela group</i>              | 1 (7.7%)             |
| <i>Morganella morganii</i>         | 1 (8.3%)             | Negative                           | 5 (38.5%)            |
| Negative                           | 1 (8.3%)             | <i>Stap. Warneri</i>               | 1 (7.7%)             |
| <i>Pseudomonas aeruginosa</i>      | 2 (16.7%)            | <i>Staphylococcus epidermidis</i>  | 1 (7.7%)             |
| <i>Staphylococcus Haemolyticus</i> | 6 (50%)              | <i>Staphylococcus haemolyticus</i> | 4 (30.8%)            |
| Total                              | 12 (100%)            | Total                              | 13 (100%)            |

**Table 3.** Distribution of antibiotic sensitivity of NGT stent swab.

| Sensitive antibiotic | Group A<br>Frequency | Sensitive antibiotic | Group B<br>Frequency |
|----------------------|----------------------|----------------------|----------------------|
| Amikacin             | 8                    | Gentamycin           | 4                    |
| Meropenem            | 8                    | Amikacin             | 3                    |
| Cotrimoxazole        | 5                    | Cefepime             | 3                    |
| Gentamycin           | 4                    | Meropenem            | 3                    |
| Cefepime             | 4                    | Cotrimoxazole        | 2                    |

**Table 4.** Comparison of colony counts.

| Colony Counts | Group A<br>Frequency | Group B<br>Frequency | p      |
|---------------|----------------------|----------------------|--------|
| Negative      | 1 (8.3%)             | 5 (38.5%)            |        |
| <100.000      | 0 (0%)               | 6 (46.2%)            |        |
| >100.000      | 11 (91.7%)           | 2 (15.4%)            |        |
| Total         | 12 (100%)            | 13 (100%)            | <0.001 |

**Table 5.** Comparison of complications

| Complication             | Group A<br>Frequency | Group B<br>Frequency | p      |
|--------------------------|----------------------|----------------------|--------|
| Urethrocutaneous Fistula | 3 (25%)              | 2 (15.4%)            |        |
| Hematoma                 | 4 (33.3%)            | 3 (21.3%)            |        |
| None                     | 5 (41.7%)            | 8 (61.5%)            |        |
| Total                    | 12 (100 %)           | 13 (100%)            | <0.001 |

Using Mann-Whitney U-test, we found a significant difference of CFU counts formation between the two groups ( $p=0.001$ ).

Statistically, the lesser CFU counts found, the lesser complication were developed ( $p=0.001$ ).

## DISCUSSION

Despite all the efforts to prevent infection after urethroplasty in hypospadias patients, infection is still happening.<sup>8</sup>

The use of stent in urethroplasty might cause connection between outer environment and neo-urethra which facilitates invasion of microorganism and eventually causes infection. The stent itself distracts the integrity of bladder and urethra's defense mechanism.<sup>9</sup>

In our department, NGT stent is used to support the neo-urethra. At post-operative day 7, we sometimes find greenish yellow stent especially at the TIP of the stent when we remove it. We suspect there is infection inside the neo-urethra that contributes to the urethra-cutaneous fistula formation.

How the infection happened is still unknown but we suspect the pathogens in the ward invade the neo-urethra through borne-air mechanism which allow the pathogens sneak through the space between the stent and neo-urethra.

Based on that, we try to decrease the colony growth of the stent by adding topical antibiotics throughout the stent before the insertion of stent during urethroplasty.

We choose gentamycin because it is a wide spectrum antibiotics that is bactericidal to both gram-positive and negative bacteria.

Due to the vast variety of hypospadias type, we only limit the subjects until the penoscrotal type and fresh cases. All subjects were operated by single surgeon using either TIP or Onlay preputial flap depending on the size of the urethral plate.

Group A were the control group that the stents were not applied by any materials. Group B were the treatment group that the stents were applied by gentamycin zalf.

We found 25 subjects that were divided into 2 groups from November 2016 until August 2017.

The result showed there was a significant decrease of colony growth and complications in treatment group.

The lack of this study was small amount of subjects and inhomogeneous subjects. Most of the subjects in group A were penoscrotal type (66.7%), while only 38,5% subjects in group B were penoscrotal type.

Despite the small amount of subjects, this study can be used as a referral to do more study to prevent infection after urethroplasty in hypospadias patients.

## CONCLUSION

Topical gentamycin application at the urethral stents in hypospadias patients performed urethroplasty significantly reduced CFU counts found at the urethral stents and thus reduced the urethra-cutaneous fistula and hematoma formation.

## REFERENCES

1. Sweet RA, Schrott HG, Kurland R. Study of Incidence of Hypospadias in Rochester, Minnesota 1940–70, and a Case Control Comparison of Etiological Factors. *Mayo Clin Proc.* 1974; 49: 52–8.
2. Navai N, Erickson B, Chao L, et al. Complications Following Urethral Reconstructive Surgery: A Six Year Experience. *Rio de Janeiro Sept./Oct. Int Braz J Urol.* 2008; 34(5).
3. Baillargeon E, Duan K, Brzezinski, et al. The Role of Preoperative Prophylactic Antibiotics in Hypospadias. *Can Urol Assoc J.* 2014; 8(7-8): 236-40.
4. Kanaroglou N, Wehbi E, Alotai A, et al. Is There a Role of Prophylactic Antibiotics after Stented Hypospadias Repair?. *The Journal of Urology.* 2013; 190: 1535-39.
5. Arshad M, Shahzad SS, Abbasi M. Applications and Complications Of Polyurethane Stenting In Urology. *J Ayub Med Coll Abbottabad.* 2006; 18(2).
6. McHugh SM, Collins CJ, Hill K, et al. The role of Topical Antibiotics Used as Prophylaxis in Surgical Site Infection Prevention. *J Antimicrob Chemother.* 2011; 66: 693–701.
7. Gentamicin sulfate. *The American Society of Health-System Pharmacists.* Retrieved Aug 15, 2015.
8. Stevanus M, Siregar S. Risk Factor for The Complication after Hypospadias Repair: A Retrospective Study. *International Journal of Urology.* 2016; 23(Suppl 1): 82.
9. Morris NS, Stickler DJ, McLean RJC. The Development of Bacterial Biofilms on Indwelling catheters. *World J Urol.* 1999; 17: 345-50.