


Original Article: Clinical Investigation**High success rate of nocturnal enuresis treatment during the stay-home period for COVID-19**Takahisa Kimiya,¹  Masayoshi Shinjoh,¹ Hiroshi Asanuma,² Tomohiro Inoguchi¹ and Takao Takahashi¹Departments of ¹Pediatrics and ²Urology, Keio University School of Medicine, Tokyo, Japan**Abbreviations & Acronyms**

ADHD = attention deficit hyperactivity disorder
CI = confidence interval
COVID-19 = coronavirus disease 2019
CR = complete response
HR = hazard ratio
ICCS = International Children's Continence Society
PR = partial response

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Objectives: To clarify whether enuresis treatment was more effective during the stay-home period for the coronavirus disease 2019 pandemic, when restrictions on activities enabled patients to concentrate on treatment.

Methods: We performed a retrospective, nonrandomized cohort study for monosymptomatic enuresis during the coronavirus disease 2019 pandemic (March–June 2020) and a 2-year comparator period (March–June 2018 and March–June 2019). Primary outcome was treatment response, defined as a change in the number of wet nights per week within 6 months following enrollment. The time-dependent occurrence of treatment response was evaluated with the Kaplan–Meier method and the log-rank test. The Cox proportional hazards regression model was used to identify risk factors for treatment response. The range of appropriate sample sizes for this primary outcome was 39–48.

Results: Of our 41 enrolled patients, 28 (68%) were male and mean age was 8.8 years. The complete response rate was 73% during the coronavirus disease 2019 pandemic period and 27% during the comparator period. Log-rank tests showed a higher cumulative incidence of complete response in the pandemic period ($P = 0.020$). Cox regression analysis identified treatment during the coronavirus disease 2019 pandemic (hazard ratio 2.533; 95% confidence interval 1.069–6.006) and dinner before 19:00 (hazard ratio 4.184; 95% confidence interval 1.56–11.252) as significantly associated with treatment response.

Conclusions: The rate of enuresis treatment response was uncommonly high during the stay-home period for the coronavirus disease 2019 pandemic. Restrictions on daily life may provide opportunities to concentrate on treatments for chronic illnesses, leading to more success.

Key words: activity restriction, chronic disease management, enuresis treatment, nocturnal enuresis, stay-home period.

Introduction

Nocturnal enuresis affects at least 10% of all 6-year-olds.^{1–7} This condition is reported to resolve in 15% of untreated patients⁸ and 70% of treated patients^{9,10} each year, but all treatments require patients and their families to adhere to the treatment regime with diligence.^{1,11} Due to the disruptiveness of the recommended treatments, the drop-out rate can be as high as 30%.¹² In practice, therefore, prior to the COVID-19 pandemic, nocturnal enuresis outpatients had a treatment response rate of only 35–50% after 1 year.^{13,14}

In response to the COVID-19 pandemic, the first state of emergency was declared on April 7, and although it was lifted on May 25, many Japanese children and parents started spending more time at home between March and May 2020.¹⁵ This lifestyle change may have permitted families to focus more attention on treatments for nocturnal enuresis.

To date, very few papers have addressed chronic disease management during the COVID-19 pandemic,¹⁶ and no papers have reported on nocturnal enuresis management during the pandemic. To clarify whether enuresis treatments were more effective during the stay-home period for the COVID-19 pandemic than before, we gathered data from medical records for a retrospective cohort study.

Methods

Study design

By reviewing medical records, we performed a retrospective, nonrandomized cohort study on 41 patients seen at two facilities in Tokyo for monosymptomatic enuresis either during the stay-home period of the COVID-19 pandemic (March–June 2020) or during a comparator period consisting of the same season in each of the previous 2 years (March–June 2018 and March–June 2019). The two facilities were Keio University Hospital and the Saiwai Pediatric Clinic, the only clinic in Tachikawa where patients with neurodevelopmental disorders are referred to from the Child and Family Support Center as a child development support facility. At Keio University Hospital, the author treated patients with nocturnal enuresis, and at the Saiwai Pediatric Clinic, the author and two other pediatricians treated them during both periods.

The definition of enuresis was bedwetting at least once a month for more than 3 months in children 5 years of age or older.¹⁷ The exclusion criteria were daytime incontinence and other lower urinary tract symptoms.¹⁷ If the same patient had been seen more than once in the selected time periods, only the last visit was considered.

At both institutions, treatment for nocturnal enuresis was administered in accordance with contemporary guidelines.^{1,11,18,19} At the first visit, we checked daytime lower urinary tract symptoms and, after ruling out the possibility of organ disease, we provided general lifestyle advice such as eating dinner earlier so as to have at least 2–3 h from dinner to bedtime, limiting water consumption in the evening, ensuring full urination before sleep, monitoring stool form, eliminating constipation, and rewarding children for dry nights. We also advised that using diapers at night is not a problem because convenience is important. If these steps had not resolved the issue after 2–4 weeks, we assessed each patient's characteristics and lifestyle and determined whether to introduce desmopressin or alarm therapy. Patients take an oral tablet of 120 µg desmopressin every night, 30 min before bedtime. The alarm, which has a moisture sensor in the form of a diaper pad, has to be used every night.

Variables

The following data were collected: patient characteristics²⁰ (sex, age, after-school activities, two-income family, neurodevelopmental disorders, history of constipation, history of urinary tract infection, family history of enuresis, using diapers at night, timing of dinner, and bedtime), frequency of bedwetting, course of enuresis treatment (time since the first visit and use of desmopressin therapy, alarm therapy, or other therapy), regular use of other medications, examination time, frequency of checkups during the research periods, and history of relapse after prior enuresis treatment. Diagnoses and treatment histories related to autism spectrum disorder,

ADHD, and learning disabilities were collected from electronic records.

Outcome measurements

Response to treatment was assessed by comparing the number of wet nights per week between enrollment and 6 months later. According to the ICCS guidelines, initial success categories were defined as follows: no response: <50% reduction in wet nights per week, PR: 50–99% reduction, CR: 100% reduction; long-term success categories were defined as follows: relapse: more than one wet night per month, continued success: no relapse for 6 months after stopping treatment.¹⁷

Statistical analysis and planned sample size

The primary outcome was initial success of enuresis treatment. We used the chi-squared test, Fisher's exact test, and Mann–Whitney *U*-test to compare the proportions of patients with each background characteristic and risk ratios among the groups. We assessed the cumulative proportion of enuresis treatment response according to the Kaplan–Meier method and made comparisons using the log-rank test. The Cox proportional hazards regression model was used to identify risk factors associated with enuresis treatment response by calculating the HRs with 95% CIs. The significance level was set at $P < 0.05$. All statistical analyses were performed using SPSS Statistics 27 (IBM, Armonk, NY, USA).

The planned sample size of 39–48 was calculated to achieve 80% power with a 0.05 significance level and 0–20% attrition²¹ to detect the difference in initial success between the stay-home and comparator periods assuming a 70% rate of response to the first choice treatment (nocturnal enuresis outpatients have a 50% response rate after 1 year, which presumably translates to 25% within a 6-month treatment period).

Ethical approval

This study and the possibility of opting out were announced to the public on the hospital website. The study was approved by the Keio University School of Medicine Ethical Committee (No. 2020-0349).

Results

Patient characteristics

Table 1 shows the characteristics of the 41 patients according to treatment period at enrollment; no patients met the exclusion criteria, and there were no dropouts during this study period. There were no significant differences in the characteristics of the two groups at the time of enrollment. The total number of nocturnal enuresis patients was 25 in 2018, 26 in 2019, and 15 in 2020; there were 15 patients during the pandemic period and 26 patients during the comparator period because the same patient was enrolled only in the last period. Among the 15 patients treated during the pandemic, the mean age was 9 years (range 5–12; 11 boys, four girls). Frequency of wet nights was 4.1/week (1–7/week), and 64.2% had a family

Table 1 Patient characteristics at enrollment

	Comparator period: 2018 and 2019 <i>n</i> = 26	Pandemic period: 2020 <i>n</i> = 15	<i>P</i> -value
Age, mean ± SD, years	8.92 ± 1.86	8.67 ± 1.66	0.622
Male sex (%)	17 (65.4)	11 (73.3)	0.734
Wet nights/week, mean ± SD	3.92 ± 2.35	4.07 ± 2.77	0.879
Duration of treatment, mean ± SD, months	12.4 ± 13.2	14.0 ± 10.0	0.389
First visit patients (%)	9 (34.6)	2 (13.3)	0.132
Family history of enuresis (%)	8/19 (42.1)	9/14 (64.2)	0.208
Neurodevelopmental disorders (%)	8 (39.8)	4 (26.7)	0.536
Constipation (%)	2 (7.7)	0 (0)	0.396
Desmopressin therapy (%)	9 (34.6)	6 (40.0)	0.730
High-dose desmopressin therapy	0	1	
Anticholinergic drug therapy	1	0	
Alarm therapy (%)	1 (3.8)	1 (6.7)	0.604
Desmopressin and alarm therapy (%)	1 (3.8)	1 (6.7)	0.604
Dinnertime, mean (range)	19:28 (19:00–21:00)	19:32 (18:00–21:00)	0.903
Dinner before 19:00 (%)	0 (0)	1 (6.7)	0.437
Bedtime, mean (range)	21:38 (20:00–24:00)	21:19 (20:00–22:00)	0.366
Interval between dinner and bedtime, h (range)	2.17 (1–5)	1.8 (1–3.5)	0.351
More than 3 h from dinner to bedtime (%)	5/18 (28)	2/14 (14)	0.318
Participation in afterschool activities (%)	11 (84.6)	11 (78.6)	0.538

history of enuresis. A total of 26.7% had a neurodevelopmental disorder (mostly mild autism spectrum disorder). One patient used methylphenidate hydrochloride for ADHD. Six patients used desmopressin, four used alarm therapy, and one used both. Ten patients (67%) started dinner before 19:00, the mean dinner–bedtime interval was 2.8 h, the proportion of patients participating in afterschool activities was 78.6%, but all were interrupted, the proportion of two-income families was 66.7%, mean duration of prior treatment was 14 months (0–30 months), and two patients (13.3%) were on their first visit. Among the 26 patients treated during the comparator period, the mean age was 9 years (range 6–12; 17 boys, nine girls). Frequency of wet nights was 3.9/week (1–7/week), and 42.1% of patients had a family history of enuresis. A total of 39.8% had a neurodevelopmental disorder (mostly mild autism spectrum disorder). Two patients used methylphenidate hydrochloride for ADHD. Sixteen patients used desmopressin, one used alarm therapy, one used both, and one used oxybutynin hydrochloride. No patients started dinner before 19:00. Mean dinner–bedtime interval was 2.1 h, the proportion of patients participating in afterschool activities was 84.6%, the proportion of two-income families was 66.7%, mean duration of prior treatment was 12.4 months (0–50 months), and nine patients (34.6%) were on their first visit.

Table 2 shows the characteristics of the 41 patients according to treatment period during March and June. The treatment period groups differed significantly in dinner start time,

Table 2 Patient characteristics during March and June

	Comparator period: March–June 2018 and 2019 <i>n</i> = 26	Pandemic period: March–June 2020 <i>n</i> = 15	<i>P</i> -value
Desmopressin therapy (%)	16 (61.5)	6 (40.0)	0.183
High-dose desmopressin therapy	0	1	
Anticholinergic drug therapy	1	0	
Alarm therapy (%)	1 (3.8)	4 (26.7)	0.051
Desmopressin and alarm therapy (%)	1 (3.8)	1 (6.7)	0.604
Examination time, mean ± SD, min	14.5 ± 10.4	10.3 ± 6.5	0.242
Frequency of checkups during the periods	2.3 ± 0.7	2.5 ± 0.8	0.498
Dinnertime, mean (range)	19:21 (19:00–21:00)	18:30 (18:00–20:00)	0.001
Dinner before 19:00 (%)	0 (0)	10 (67)	<0.001
Bedtime, mean (range)	21:30 (20:00–23:00)	21:24 (20:00–23:00)	0.331
Interval between dinner and bedtime, h (range)	2.08 (1–4)	2.8 (2–4.5)	0.030
More than 3 h from dinner to bedtime (%)	6/18 (33)	9/14 (64)	0.082
Participation in afterschool activities (%)	11 (84.6)	0 (0)	<0.001
Use of diapers at night (%)	21/23 (91.3)	9/15 (60.0)	0.029
Treatment during state of emergency (%)	0 (0)	14 (93.3)	<0.001

likelihood of starting dinner before 19:00, dinner–bedtime interval, nighttime diaper use, and, naturally, likelihood of visiting during a state of emergency and/or participation in afterschool activities ($P < 0.05$). During the pandemic period, six patients used desmopressin, four used alarm therapy, and one used both. Ten patients (67%) started dinner before 19:00, the mean dinner–bedtime interval was 2.8 h, all afterschool activities were interrupted, and rate of nighttime diaper use was 60%. Mean examination time was 10.3 min and frequency of checkups was 2.5 times. During the comparator period, 16 patients used desmopressin, one used alarm therapy, one used both, and one used oxybutynin hydrochloride. No patients started dinner before 19:00, the mean dinner–bedtime interval was 2.1 h, and rate of nighttime diaper use was 91.3%. Mean examination time was 14.5 min and frequency of checkups was 2.3 times.

Treatment response

Among patients treated during the pandemic, within 6 months, 11 achieved CR (73%) and three achieved PR; thus, 14 out of 15 patients (93%) achieved a response of any kind, as Table 3 shows. Of four patients with neurodevelopmental disorders, three achieved a response of any kind. Eight of the 11 CR patients had continued success; two were lost to follow-up. The remaining patient stopped alarm therapy and relapsed to

three wet nights per month; general lifestyle advice reduced this to one wet night per month within 3 months.

One patient who achieved PR during the pandemic had previously been treated with desmopressin, but only on the weekends because of extracurricular activities on weekday evenings. At that time he had six wet nights per week. During the stay-home period, in contrast, the patient was able to take desmopressin every night, and his wet nights per week fell to three within 3 months and then to one within 6 months.

During the comparator period, seven patients achieved CR (27%) and eight achieved PR; thus, 15 out of 26 (58%) achieved a response of any kind. Of eight patients with neurodevelopmental disorders, seven achieved a response of any kind. Five out of seven CR patients had continued success; the other two were lost to follow-up.

The response rate was significantly higher during the pandemic (CR 73%, PR 93%) than during the comparator period (CR 27%, PR 58%), even in a sensitivity analysis excluding first-visit patients (pandemic: CR 77%, PR 92% vs comparator: CR 29%, PR 59%). Figure 1 shows the Kaplan–Meier curve for cumulative CR rates and total response rates according to treatment period. A log-rank test confirmed a significantly higher response rate during the pandemic ($P = 0.020, 0.003$).

Risk factors associated with treatment effects

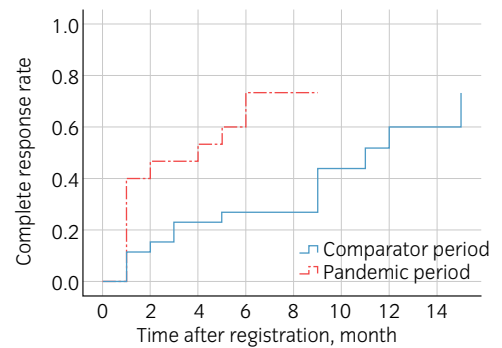
As Table 4 shows, treatment during the pandemic (HR 2.533; 95% CI 1.069–6.006), treatment during a state of emergency (HR 3.036; 95% CI 1.274–7.233) and dinner before 19:00 (HR 4.184; 95% CI 1.56–11.252) were significantly associated with both CR and total response. Frequency of wet nights at first visit was significantly associated only with CR, while nighttime diaper use and participation in afterschool activities were significantly associated only with total response.

Table 3 Response to enuresis treatment after 6 months

	Comparator period: March–June 2018 and 2019 <i>n</i> = 26	Pandemic period: March–June 2020 <i>n</i> = 15	Relative risk	95% CI	<i>P</i> -value
Total response (%)	15 (58)	14 (93)	0.618	0.433–0.882	0.016
PR (%)	8 (31%)	3 (20%)			
CR (%)	7 (27%)	11 (73%)	0.367	0.182–0.742	0.004
Continued success (%)	5/5 (100%)†	8/9 (89%)‡			
No response (%)	11 (42%)	1 (7%)			

PR: 50–99% reduction. CR: 100% reduction. Continued success: no relapse in 6 months after cessation of treatment. †Two were lost to follow-up. ‡Two were lost to follow-up.

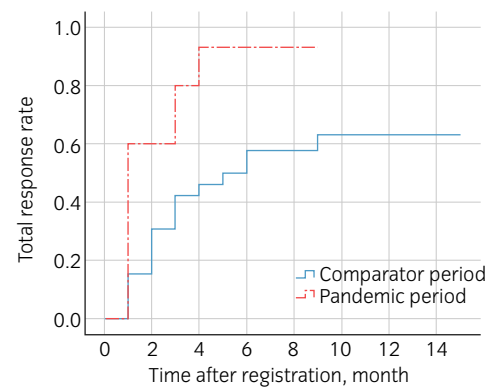
(a) Complete response



Number at risk

Pandemic period	15	9	8	6	4	0	0	0
Comparator period	26	23	20	17	13	7	6	3

(b) Total response



Number at risk

Pandemic period	15	6	3	1	1	0	0	0
Comparator period	26	22	15	13	8	3	3	1

Fig. 1 Kaplan–Meier curve for cumulative response to enuresis treatment during the COVID-19 pandemic and the comparator period. (a) Log-rank test revealed that the CR rate was significantly higher during the COVID-19 pandemic period ($P = 0.020$). (b) Log-rank test revealed that the total response rate was significantly higher during the COVID-19 pandemic period ($P = 0.003$).

Discussion

This study demonstrated for the first time that enuresis treatment response rates were significantly higher during the COVID-19 pandemic than they were during ordinary times, probably because the stay-home policies in place during the pandemic allowed families to focus more of their attention on treatment. The factors that were significantly associated with treatment response were treatment during the COVID-19 pandemic, treatment during the state of emergency, and dinner before 19:00.

Table 4 Cox regression analysis of enuresis treatment response

	CR		Total response	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Treatment during COVID-19 pandemic	2.533 (1.069–6.006)	0.035	2.597 (1.229–5.491)	0.012
Treatment during state of emergency	3.036 (1.274–7.233)	0.012	2.359 (1.116–4.985)	0.025
Dinner before 19:00	4.184 (1.556–11.252)	0.005	3.045 (1.254–7.393)	0.014
Participation in afterschool activities	0.456 (0.158–1.317)	0.147	0.368 (0.138–0.976)	0.045
Dinnertime	0.513 (0.244–1.079)	0.078	0.561 (0.295–1.067)	0.078
Interval between dinner and bedtime	1.267 (0.717–2.239)	0.415	1.334 (0.809–2.201)	0.259
More than 3 h from dinner to bedtime	2.088 (0.787–5.540)	0.139	1.908 (0.829–4.392)	0.129
Number of wet nights/week	0.746 (0.610–0.913)	0.004	0.908 (0.785–1.052)	0.199
Desmopressin therapy	0.946 (0.413–2.167)	0.895	0.840 (0.409–1.724)	0.634
Alarm therapy	1.967 (0.726–5.332)	0.184	1.651 (0.630–4.332)	0.308
Use of diapers at night	0.411 (0.162–1.042)	0.061	0.396 (0.168–0.933)	0.034

The rate of CR to enuresis treatment was 73% during the COVID-19 pandemic, in striking contrast to the 27% rate during the comparator period. Regardless of whether aggressive treatments such as desmopressin therapy and alarm therapy are used, the CR rate among all enuresis outpatients is reported to be 35–50% after 1 year of treatment;^{13,14} therefore, the present study's CR rate of 27% over the 6-month comparator period is reasonable, as it represents approximately half of the 50% of patients expected to achieve a CR over 1 year.

According to previous reports on aggressive treatments, the CR and total response rates to desmopressin treatment are as high as 30% and 70%, respectively, but nearly 70% of patients who initially respond to desmopressin experience relapse upon interruption of treatment, and many patients find it necessary to skip medication to prevent water intoxication on days when evening activities prevent water restriction.^{1,9} Alarm therapy, meanwhile, has a high CR rate of 70%,¹⁰ but it also has a high withdrawal rate of 30%,¹² and cannot be introduced in the first place without strong motivation on the part of the patient and the family.^{1,11} General lifestyle advice and behavioral therapy are less effective than desmopressin therapy and alarm therapy.²²

We speculate that the stay-home policies in place during the pandemic allowed families to take time to focus more of their attention on treatment.¹⁵ During the COVID-19 pandemic, hospital and clinic visits to treat enuresis and other chronic pediatric diseases tended to be put off, yet at the same time, families tended to adhere more strictly to their treatment regimens. Thus, pandemic-related policies may have indirectly enabled higher treatment effects.

Treatment during the COVID-19 pandemic, treatment during the state of emergency, and dinner before 19:00 were significantly associated with response to treatment for nocturnal enuresis. It is likely that a larger proportion of families were able to comply with early dinnertime as recommended in the general lifestyle advice for nocturnal enuresis because extracurricular activities, in which approximately 80% of the children had previously been involved, were stopped, and because approximately 70% of two-income households had at least one parent who switched to telework or stopped

working during the pandemic. In addition, four patients took advantage of the stay-home period to introduce alarm therapy, which led to CR as long as the therapy was continued. Some patients found it easier to comply with water restrictions because their extracurricular academic activities were stopped, which tended to make their treatment more effective. In this study, alarm therapy was a factor related to high response rate, although this trend was not significant because of our sample size.

This study has some limitations. First, because the number of patients was small, multivariate analysis could not be performed on the risk factors identified by univariate analysis, that is, treatment during the COVID-19 pandemic, treatment during the state of emergency, and dinner before 19:00. It is reasonable, however, to assume that stay-home policies led to higher compliance with enuresis treatments and earlier dinnertimes, which led, in turn, to lower frequencies of wet nights. We believe that the number of patients was appropriate for this study, as too many samples can be inappropriate for the proper evaluation of our primary outcome. A second limitation is that, since there were few new patients during the COVID-19 pandemic period, the patients seen during this period are more likely to have been treated previously and to have improved over time. We believe, however, that our conclusions remain reasonable because, as described in the Results section, the mean durations of treatment were similar in the two periods, and we found similar results even in a subanalysis excluding all first-visit patients from both periods. Third, many of these enrolled patients have neurodevelopmental disorders, which is reflective of the facilities they attended. The success rate of patients with nocturnal enuresis in the general population is unclear when applying the same analysis. Fourth, significantly more patients in the comparator period used diapers at night, suggesting a more severe patient population. However, since there was no difference in the frequency of wet nights between both periods, this is not always the case. Fifth, the total number of nocturnal enuresis patients decreased during the stay-home period, so it is probable that only highly motivated patients visited. One limitation is a lack of clear data on compliance with therapy regimens and

water restriction. To avoid these issues in future studies involving prospective multicenter joint research, including the functional bladder capacity and nocturnal urine volume as patient background and the compliance rate of water restriction, desmopressin therapy, and alarm therapy as indicators of treatment motivation is needed.

We confirmed a high rate of response to nocturnal enuresis treatment during the stay-home period of the COVID-19 pandemic. Situations that place restrictions on daily life, such as the COVID-19 pandemic, can be good opportunities to focus on treatments for chronic illnesses and improve their success rates.

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Author contributions

Takahisa Kimiya: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing. Masayoshi Shinjoh: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing. Hiroshi Asanuma: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing. Tomohiro Inoguchi: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing. Takao Takahashi: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Conflict of interest

None declared.

Approval of the research protocol by an Institutional Reviewer Board

The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Keio University School of Medicine Ethical Committee, Approval No. 2020-0349.

Informed consent

N/A. This study and the possibility of opting out were announced to the public on the hospital website.

Registry and the Registration No. of the study/trial

N/A.

Animal studies

N/A.

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