2004

FINAL NARRATIVE REPORT

GRANT TITLE: NON ANTIBIOTIC ALTERNATIVES FOR THE PREVENTION AND TREATMENT OF URINARY TRACT INFECTIONS FOLLOWING SCI.

GRANT NUMBER: #01 –SRC-3011-N-0

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NON ANTIBIOTIC ALTERNATIVES FOR THE PREVENTION AND TREATMENT OF URINARY TRACT INFECTIONS FOLLOWING SCI.

Grant Number: 01 –SRC-3011-N-0

AIMS OF STUDY:

There were two parts of this grant: prevention studies and treatment studies. The aim of the prevention study was to determine the effectiveness of cranberry, uva ursi and echinacea compared to a placebo (normal saline) at *preventing* acute UTI's. The aim of the treatment study was to determine the effectiveness of cranberry, and uva ursi and echinacea compared to an antibiotic in *treating* acute UTI's.

PREVENTION STUDIES

AIM 1: To determine the effectiveness of cranberry, uva ursi and echinacea compared to a placebo (normal saline) at *preventing* acute UTI's.

DESIGN: Prospective randomized controlled animal study.

METHODS: This study was done in a well established SCI animal model, the Sprague Dawley rat, since many variables such as bladder function and management make human studies in those with SCI difficult. All procedures and surgeries were approved by the Animal Welfare Subcommittee of the East Orange Department of Veterans Affairs Medical Center.

60-day-old female Sprague Dawley rats (Charles River, Wilmington Massachusetts) were housed for two weeks prior to surgery. Lights were on from 0600 to 1800 hours and animals had free access to Purina Rodent chow and tap water.
Rats were deeply anesthetized with sodium pentobarbital (35 mg./100 gm. body weight). A laminectomy was performed at the level of the ninth vertebrae. The spinal cord was exposed and severed under direct visualization. For purposes of SCI care approximately 20-40 animals were done at any one time.

Following surgery, SCI rats were creded three times a day to express urine from the bladder. This was continued until the animals came out of spinal shock and were voiding effectively on their own with minimal amounts in their bladder to crede. Prophylactic antibiotics (20,000 units procaine penicillin and 25 mg dihydrostreptomycin) were administered the day of and one day post surgery. Post operatively, animals were singly housed in shoe box cages and had free access to Purina rodent chow and tap water.

One week post SCI, a midstream urine sample was obtained using crede. The sample was sent to culture and sensitivity (UA C&S) was taken to confirm that there was no

urinary tract infection. A urine was considered to be positive for a urinary tract infection if there was the presence of bacteria and the presence of white blood cells (> 10 WBC's per high field).

For the prevention studies, animals *without* a UTI were randomized into one of 4 groups: control, cranberry, echinacea, or uva ursi, with weekly urine analysis and culture and sensitivity (UA C&S). The non antibiotic alternative groups had 2-3 daily gastric gavages of 2 ml. of water mixed with the non antibiotic alternative. The control group – had 2 daily gastric gavages of 2 ml. of water only.

Dosage of each antibiotic and non antibiotic alternative used for treatment was extrapolated, based on rats weighing 250 grams and suggested doses for humans (weighing 70 kg). Suggested human dosages: cranberry 500 mg three times a day, echinacea 500 mg twice a day, uva ursi 2-3 ml tincture three times a day.

Animals underwent weekly UA C&S at 1 week, 4 weeks and then monthly for a total of 5 months. It was determined which animals did and did not have a urinary tract infection and this was recorded. When an animal was found to have an infection, it was dropped from the study and considered to be a prevention treatment failure.

RESULTS:

% OF ANIMALS DEVELOPING URINARY TRACT INFECTIONS

Time interval	1 week	3 weeks	2 months	3 months	4 months	5 months
Controls	0 %	7 %	0 %	0 %	0%	7 %
Uva Ursi	25%	7%	0%	33%	0%	7%
Echinacea	-	0%	-	73%	-	0%
Cranberry	24%	20%	0%	41%	0%	0%

370 urine samples obtained. We found that very few SCI control animals (no alternative prevention agents) developed urinary tract infections. This had not been the case using a similar SCI animal model in other studies (SCI fertility). Perhaps the difference is that female animals which were used in this study (because it is easier to crede their bladders compared to male rats) were less likely to develop UTI's than males. (I had used male rats in my SCI male fertility studies). Another possibility is that there was more attention paid to bladder crede (emptying), since this was a UTI study and animals

were getting frequent urine samples. Whatever the reason, despite a large number of animals and urine samples, it was not possible to determine the effectiveness of the alternative treatments. Of interest is that animals taking echinacea for 3 months had significantly more UTI's than controls; however, this was not true for any other time segments.

CONCLUSIONS: The effectiveness of non antibiotic alternatives at preventing UTI's in this animal model was not possible because UTI's occur very infrequently in the SCI female Sprague Dawley rat model.

TREATMENT STUDIES

AIM 2: To determine the effectiveness of cranberry, and uva ursi and echinacea compared to an antibiotic in *treating* acute UTI's.

DESIGN: Prospective randomized controlled animal study.

METHODS: This study was done in a well established SCI animal model, the Sprague Dawley rat, since many variables such as bladder function and management make humans studies in those with SCI difficult. All procedures and surgeries were approved by the Animal Welfare Subcommittee of the East Orange Department of Veterans Affairs Medical Center.

60-day-old female Sprague Dawley rats (Charles River, Wilmington Massachusetts) were housed for two weeks prior to surgery. Lights were on from 0600 to 1800 hours and animals had free access to Purina Rodent chow and tap water.
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One week post SCI, a midstream urine sample was obtained using crede. The sample was sent for a urine analysis and culture and sensitivity (UA C&S) was taken. A urine was considered to be positive for a urinary tract infection if there was the presence of bacteria and the presence of white blood cells (> 10 WBC's per high field); Animals with a urine sample consistent with a urinary tract infection were randomized into one of 4 treatment groups: amoxicillin, cranberry, echinacea, or uva ursi. Dosage of each antibiotic and non antibiotic alternative used for treatment was extrapolated, based on rats weighing 250 grams and suggested doses for humans (weighing 70 kg). Suggested

human dosages: cranberry 500 mg three times a day, echinacea 500 mg twice a day, uva ursi 2-3 ml tincture three times a day.

After 7 days of the non antibiotic alternative and a 3 day washout, a urine analysis and repeat urine sample were obtained. Since WBC's signify tissue invasion, a UTI was considered to be resolved if the repeat urine sample showed the absence of WBC even if bacteria were still present. (Figure 3 and Figure 4).

Data was analyzed using Barnard's unconditional test of superiority.
The two outcome measures were the proportion of rats showing the resolution of bacteriuria and the proportion of rats demonstrating a resolution of WBC's.

RESULTS: *Bacteria Resolution*: amoxicillin- 42%, uva ursa - 79% , echinacea- 0% and cranberry –0%. Statistical analysis: amoxicillin, uva ursi, not different in effectiveness at bacterial resolution ($p=0.1$) and statistically superior to echinacea and cranberry ($p = 0.003$, $p = 0.0001$) . *WBC Resolution*: amoxicillin - 76%, uva ursa - 67% , echinacea - 67% and cranberry - 19%. Statistical analysis: amoxicillin, uva ursi, and echinacea not different in effectiveness ($p = 0.23$, $p = 0.83$). Amoxicillin, uva ursi, and echinacea statistically superior to cranberry ($p = 0.01$, $p = 0.003$, $p= 0.04$).

CONCLUSIONS: Amoxicillin, uva ursi and echinacea had similar results in the resolution of WBC's (acute UTI's). Cranberry was not effective in treating acute UTI's. This study justifies further studies regarding the role of uva ursi and echinacea in treating acute UTI's in those with SCI.

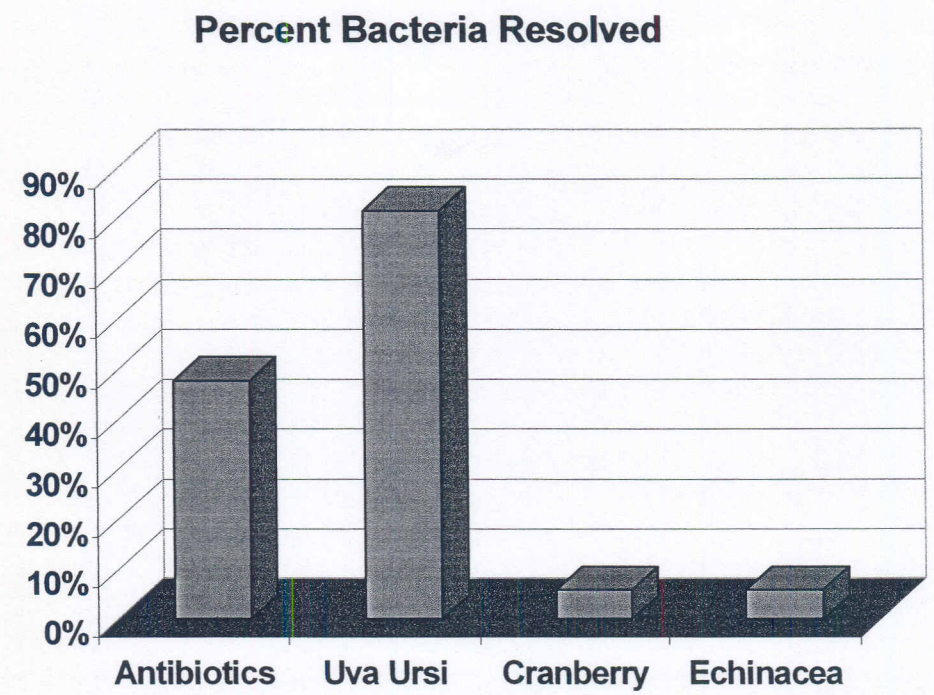

Figure 1. Impact of various agents on bacterial resolution.

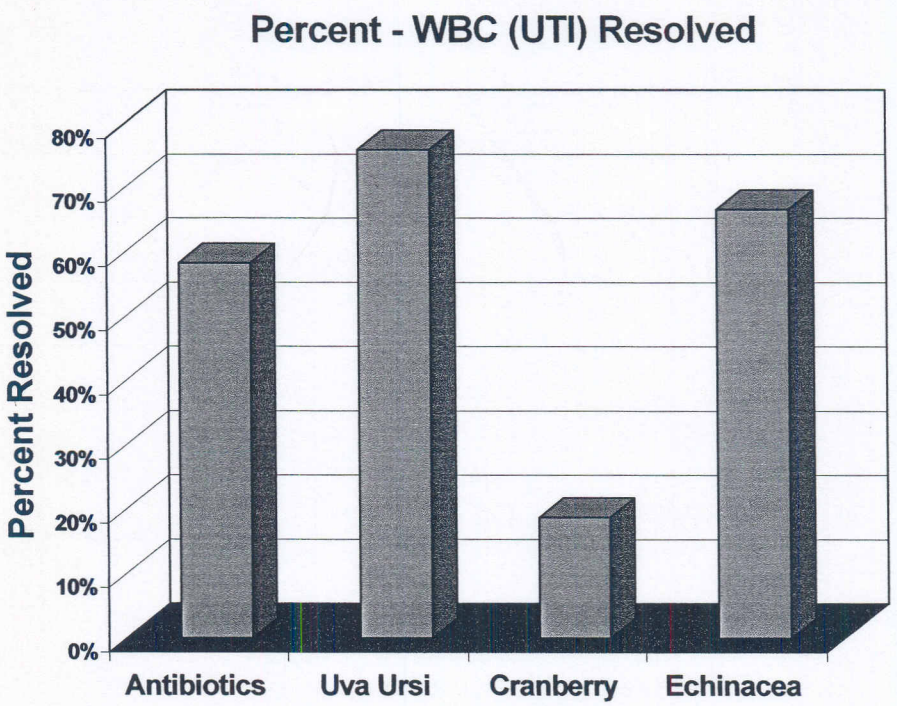

Figure 2. Impact of various agents on WBC resolution.

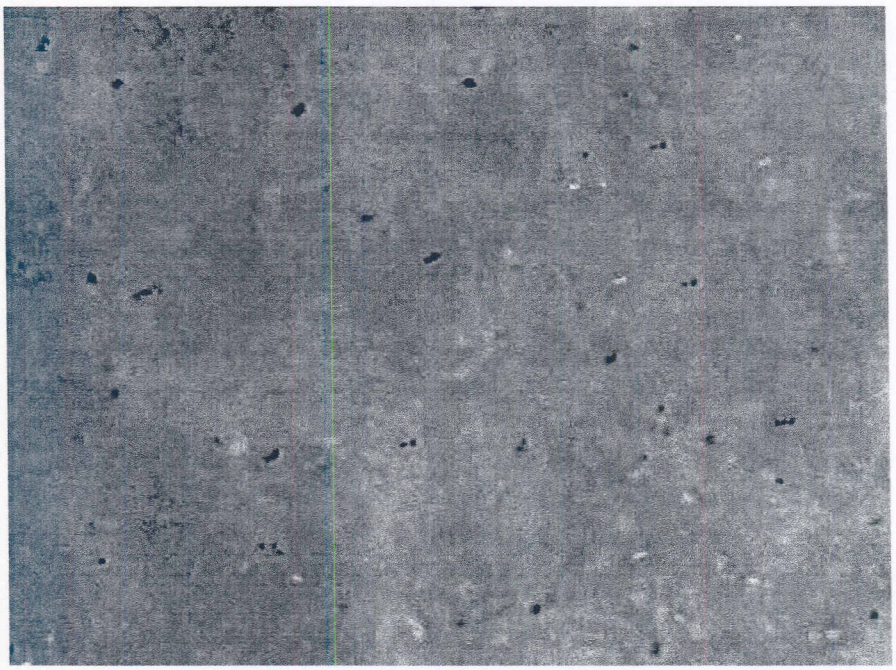

Figure 3. Example of persistent bacteria but no WBC's.

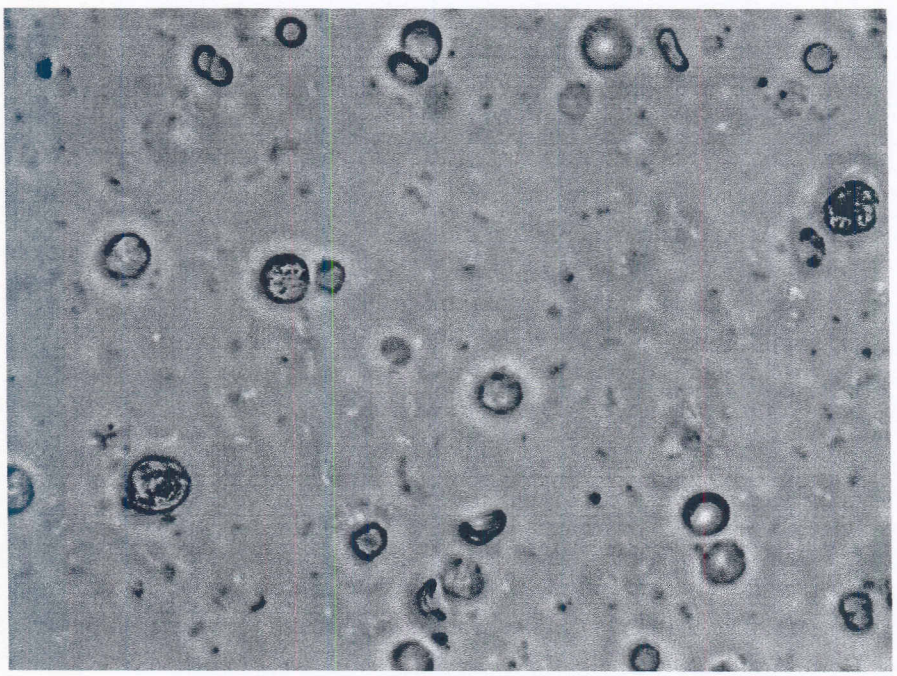

Figure 4. Example of persistent bacteria and WBC's.

SUCCESS:

The most important findings of this study was that the commonly used non antibiotic alternatives uva ursi and echinacea were effective at treating urinary tract infections.

CHALLENGES: The main challenge of this study was attempting to conduct prevention studies. The SCI animals in general, particularly the controls (no agent given) rarely developed UTI's. Therefore determining the effectiveness of non antibiotic alternatives was not possible despite having a large number of animals and urine samples in the prevention studies.

IMPLICATIONS FOR FUTURE RESEARCH:

To determine if uva ursi and echinacea are effective in treating UTI in humans with SCI
To determine if uva ursi and echinacea are effective in treating all types of bacteria.
To determine the optimum dose of uva ursi and echinacea.
To determine the optimum duration of treatment.
The female Sprague Dawley rat is not a good animal model for prevention studies.
Despite many variables in humans, consideration should be given to proceed to human studies for prevention studies since SCI rats have infrequent bladder infections post SCI.
To develop a SCI animal model to study infections post SCI (such as inoculation of bladders with bacteria, differences in UTI's in male versus female rats)

PLANS TO CONTINUE RESEARCH:

We have been conducting a human prevention study on the effectiveness of cranberry at preventing urinary tract infections. Of interest is that our results, like that in the animal treatment studies, show that cranberry is not effective at preventing urinary tract infections.

We plan to investigate the above questions regarding effectiveness of antibiotics in our animal model. We are considering submission of the grant to the PVA Spinal Cord Research Foundation, Department of Veterans Affairs.

PUBLICATIONS AND PRESENTATIONS:

Presentations

LINSENMEYER, T.A., MILLIS S, : Effectiveness of a Non-Antibiotic Alternative In Treating Urinary Tract Infections; Annual Meeting American Paraplegia Society, Las Vegas, NV 2002.

LINSENMEYER, T.A.: Effectiveness of Non Antibiotic Alternatives in Treating Urinary Tract Infections Following Spinal Cord Injuries. Annual Meeting American Paraplegia Society, Las Vegas, NV.; Sept. 2003.

LINSENMEYER, T.A.: Non Antibiotic Alternatives to Treat UTI's. New Jersey Commission.; New Brunswick, New Jersey Oct. 2003.

LINSENMEYER, T.A.:, Scott Millis, Ph.D. Effectiveness Of Cranberry Supplement In Preventing and Treating Acute UTI's Following SCI.
Submitted for presentation at the 2005 American Paraplegia Society annual meeting

Publications

LINSENMEYER T.A., MD, Scott Millis, PhD., M.Ed.: Effectiveness of a Non-Antibiotic Alternative In Treating Urinary Tract Infections; J. of Spinal Cord Medicine (Abstract) Vol. 25 220:2002.

LINSENMEYER, T.A.: Effectiveness of Non Antibiotic Alternatives in Treating Urinary Tract Infections Following Spinal Cord Injuries. J Spinal Cord Medicine (Abstract) Vol. 26 284: 2003.

LINSENMEYER T.A., MD, Scott Millis, PhD., M.Ed. Non Antibiotic Alternatives For The Treatment Of Urinary Tract Infections Following Spinal Cord Injury.
Manuscript submitted to: *The Journal of Spinal Cord Medicine.*