Cysticlean® (CYS), is a special American cranberry extract with a very high proanthocyanidins (PAC) concentration (240 mg per capsule or sachet) which has been available in Europe since 2007. Several preclinical studies have proven that CYS has a high anti-adhesion activity (AAA) of up to 90% against Escherichia coli (Ec). This AAA is PAC concentration related: the more PAC the more AAA. It is available in boxes of 10, 30 and 60 capsules and 30 sachets. AAA activity has been proven to be related to its efficacy in treating and preventing urinary tract infections (UTI). Several clinical studies have been conducted and published with CYS treating and preventing UTI in children with urological congenital diseases, fertile and post-menopausal women, post-coital infections and women and elderly men including up to 608 patients (242 children, 160 elderly, 206 adults) giving a very good profile of safety and efficacy. No serious adverse reaction/side effects have been reported from clinical studies or from the market due to the administration of CYS. The CYS profile strongly suggests it could be an alternative to antibiotic treatment at a time when such treatment is failing due to the continuous increase in bacteria antibiotic resistance.
<table>
<thead>
<tr>
<th>Title of the study</th>
<th>Author</th>
<th>Where</th>
<th>When</th>
<th>Patients n°</th>
<th>Conclusions</th>
<th>Published</th>
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<tr>
<td>Concentration-Dependent Effect on Adherence of Escherichia Coli to Bladder Epithelial Cells of Cysticlean® Capsules (240 Mg/Capsule of Proanthocyanidins)</td>
<td>E Risco Rodríguez et al.</td>
<td>Harlan, Egara, Spain</td>
<td>2015</td>
<td>Pre-clinical</td>
<td>CYS capsules (240 mg/capsule of PACs) induces a dose-dependent significant decrease in the number of E. coli adhered. Previous clinical assays showed that CYS is a product highly recommended in the prophylaxis and treatment of UTIs. The present study confirms that number of PACs is very important to achieve greatest effectiveness of the cranberry products.</td>
<td>The Internet Journal of Microbiology. 2015 Volume 13 Number 1. DOI: 10.5580/I-JMB.33094</td>
</tr>
<tr>
<td>Evaluation of Cysticlean® capsules, a cranberry extract with high anti-adhesion activity, as monotherapy in uncomplicated cystitis: an observational pilot study</td>
<td>Isidre Bonet et al.</td>
<td>Clinic Diagonal, Barcelona, Spain</td>
<td>2015</td>
<td>30</td>
<td>21 patients were successfully cured with CYS treatment only (70%) and 9 patients needed antibiotic to cure their UC. 82.35% of women and 53.85% of men did not need antibiotic to be cured</td>
<td>Rev Electron Biomed J Electron J Biomed 2015;2</td>
</tr>
<tr>
<td>Proanthocyanidins American cranberry extract as an alternative to antibiotic prophylaxis in pediatric patients with lower urinary tract malfunction</td>
<td>Martin-Crespo RM et al.</td>
<td>Uro-pediatric Depart at Toledo Hospital Complex, Barcelona, Spain</td>
<td>2015</td>
<td>101 children</td>
<td>90.70% did not had an infection after 1 y treatment with Cysticlean. Only 2.97% of patients (3 patients) suffered of episodes of UTI. One case has vesicostomy, one neurogenic bladder and the other dysfunctional voiding. Antibiotic prophylaxis was re-established in these patients.</td>
<td>To be published</td>
</tr>
<tr>
<td>High Proanthocyanidins American Cranberry Extract in Pediatric Urology: An Efficacy and Tolerability study</td>
<td>Miguélez Lago, Carlos et al.</td>
<td>Hosp. Clinic Santa Elena, Málaga, Spain</td>
<td>2011</td>
<td>74 children</td>
<td>90% of patients did not had a UTI during the treatment period, 6.0% of patients had less UTI than before to start CYS treatment and UTI infection rate did not change in 3.3% of patients. No adverse events/side effects related to CYS were reported.</td>
<td>To be published</td>
</tr>
<tr>
<td>Cranberries in The Treatment of Cystitis. An Observational Study</td>
<td>Isidre Bonet et al.</td>
<td>Clinic Diagonal, Barcelona, Spain</td>
<td>2008</td>
<td>83</td>
<td>Administering a cranberry extract with a high PAC content during a 3-month period to patients with recurrent UTI coincided with a noticeable decrease (&gt;90%) in the usual re-incidence rate of these infections</td>
<td>Urol Integr Invest 2008;13(3):214-217</td>
</tr>
<tr>
<td>Observational study of using American cranberry extract rich in proanthocyanidins (Cysticlean®) to treat recurrent urinary tract infections</td>
<td>A. Collado, et al.</td>
<td>Institut Valenciano de Oncología (IVO), Valencia, Spain</td>
<td>2009</td>
<td>78</td>
<td>The 3-month long course of CYS in patients with recurrent infections was proven to be a well-tolerated treatment, showing a very low rate of re-infections (14%) compared to the previous reports</td>
<td>Urol Integr Invest 2009;13(3):214-217</td>
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<tr>
<td>Cysticlean®, a highly PAC standardized content in the prevention of recurrent urinary tract infections: an observational, prospective, cohort study (Postcotal infections PCUTI)</td>
<td>Francisco Sánchez Ballester, et al.</td>
<td>Hospital General de Valencia, Spain</td>
<td>2013</td>
<td>20</td>
<td>The number of PCUTI in the previous 3 m prior to start CYS treatment was 2.8 ±1.3 and it was reduced at 0.2±0.5 at month 6 (p&lt;0.001), which represents a 93% improving</td>
<td>BMC Urology 2013, 13:28 DOI:10.1186/1471-2490-13-28</td>
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<tr>
<td>Cysticlean and Prophylaxes of Recurrent Urinary Tract Infections: Is the age a limiting factor?</td>
<td>Fernando Rodríguez Escobar, et al.</td>
<td>CYMA, Barcelona, Spain</td>
<td>2016</td>
<td>161</td>
<td>No significant differences were found between groups A and B re re-infection rate at 3 weeks of CYS treatment (A=93%; B=10,6%) at 3 m (A=11,8%;B=13,9%). Symptoms were more frequent in group B but only microhematuria was statistically significantly higher in this group compared to group A (p&lt;0.05). Number of patients without reinfection at 3 m treated with CYS was similar in both groups.</td>
<td>Revista Médica Electrónica Portales médicos.com ISSN 1886-8924</td>
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<tr>
<td>Clinical Evaluation of a Cranberry Extract in the Treatment of Recurrent Cystitis in Patients over 70 y old: The GerHogar Cysticlean® Study A Prospective Observational Study</td>
<td>J. Macías, et al.</td>
<td>Gerhogar, University of Salamanca, Spain</td>
<td>2018</td>
<td>160</td>
<td>31 of 38 patients of the group 1 treated for 1 m were successfully treated with CYS and 100 patients of 122 of the group 2 were successfully treated and followed up to 10 m. (81,52% and 81,96% respectively). Low glomerular filtration rate and high HÜGE score suggest higher risk of re-infection in females than males.</td>
<td>Submitted</td>
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<tr>
<td>Uncomplicated Cystitis Treated with High Proanthocyanidins Cranberry Concentration in Patients Aged 70 years old and below with Recurrent Urinary Tract Infections</td>
<td>Jesús-José Cuadrado Blanco, et al.</td>
<td>Gerhogar, University of Salamanca, Spain</td>
<td>2018</td>
<td>27</td>
<td>21 patients (78%) did not have any urinary infection along the study period. 4 males and 2 females had one. Neither non-infected patients nor infected patients showed any significant difference on its glomerular filtration rate, eGfr, glomerular filtration rate, Blood Creatinine, Blood urea and Huge before and after the treatment</td>
<td>Submitted</td>
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CONCENTRATION-DEPENDENT EFFECT ON ADHERENCE OF ESCHERICHIA COLI TO BLADDER EPITHELIAL CELLS OF Cysticlean® CAPSULES (240 MG/CAPSULE OF PROANTHOCYANIDINS)

E Risco Rodríguez, L A Álvarez-Sala Walther, V C Ramos, I Bonet
The Internet Journal of Microbiology. 2015 Volume 13 Number 1.
DOI: 10.5580/IJMB.33094

Abstract

Background: the proanthocyanidins (PACs) are the main components of cranberry (fruit of Vaccinium macrocarpon Aiton), and their content determines the effectiveness in the urinary tract infections (UTIs). The activity of PACs is related to inhibition of bacterial adherence. Cysticlean® (CYS) is a cranberry extract product with a high quantity of PACs (240 mg/capsule of PACs). CYS is used in the prevention and treatment of recurrent UTIs. The aim of this study is the comparison of different concentrations of CYS capsules on adherence of Escherichia coli to bladder epithelial cells.

Methods: In vitro, E. coli pre-incubated in different concentrations of CYS capsules was incubated with human urinary bladder carcinoma cells (T24 cells) for 1 hour and the number of bacteria adhered to cells was recorded.

Results: CYS has demonstrated a dose-dependent inhibition of bacterial adherence. At concentrations of 5, 25, 75 and 137 mg PACs/mL, CYS decreases the number of bacteria adhered to epithelial cells by 17%, 52%, 76 and 89%, respectively.

Conclusions: CYS capsules (240 mg/capsule of PACs) induces a dose-dependent significant decrease in the number of E. coli adhered. Previous clinical assays showed that CYS is a product highly recommended in the prophylaxis and treatment of UTIs. The present study confirms that number of PACs is very important to achieve greatest effectiveness of the cranberry products.

EVALUATION OF Cysticlean® CAPSULES, A CRANBERRY EXTRACT WITH HIGH ANTI-ADHESION ACTIVITY, AS MONOTHERAPY IN UNCOMPLICATED CYSTITIS: AN OBSERVATIONAL PILOT STUDY

Ester Risco Rodríguez Pharm. PhD. Humberto Suárez MD. PhD., Isidre Bonet MD. PhD., Jesús-José Cuadrado Blanco MD. PhD.

Summary:

Background: Cysticlean® (CYS) is a cranberry extract product with a high quantity of proanthocyanidins (240 mg/capsule) with a significant dose-dependent anti-adhesion activity of Escherichia coli (EC) adhered to uroepithelial cells. Previous clinical assays showed that CYS is a product highly recommended in the prophylaxis and treatment of UTIs. The aim of this study is the evaluation of CYS as an alternative to antibiotics to treat uncomplicated cystitis.

Material and Methods: This observational study included 30 consecutive ambulatory patients (17 women and 13 men), who were diagnosed of uncomplicated cystitis (UC) and agreed to participate in this observational study. Patients were informed to come to visit the doctor again after 15 days after CYS treatment was started (1 capsule of CYS every 12 h daily) and immediately if signs/symptoms did not disappear. In this case, CYS® was stopped and patients treated with antibiotic.

Results: 21 patients were successfully cured with CYS treatment only (70%) and 9 patients needed antibiotic to cure their UC. 82.35% of women and 53.85% of men did not need antibiotic to be cured. No significant differences at baseline were found regarding signs/symptoms severity between those patients cured with extract alone and those who needed antibiotic. No side effects/adverse reactions were reported.

Conclusions: These preliminary data strongly suggest that CYS could be considered as an alternative to antibiotics for a 1st line treatment of UC. Further clinical studies to confirm whether CYS could be an alternative to antibiotic treatment for UC and this approach could contribute to reduce world-wide growing antibiotic resistance.
TREATMENT OF PEDIATRIC URINARY INFECTIONS WITH AMERICAN CRANBERRY EXTRACT.

J.M. Garat Barredo
Pediatric Urology Unit. Fundacio Puigvert.
Barcelona, Spain
Acta Pediátrica Española. 2011; 69(3): 117-120

Abstract

Introduction & Objectives: In our search for alternatives to antibiotic chemoprophylaxis to prevent pediatric urinary infections, we have started to use a concentrated extract (Cysticlean®) of American red cranberries containing high concentration of proanthocyanidins. The before mentioned inhibit the adherence of P-fimbriated Escherichia coli to the urinary tract wall.

Objectives: To observe the effectiveness and tolerance of a concentrated extract of cranberries in children with frequent urinary tract infections.

Material and methods: We selected groups of patients with frequently recurrent urinary infections, with no malformative systemic pathologies and either neuropathic bladder, lithiasis or renal failure. The observational study was conducted over one year in 62 children from 5 to 17 years old.

Results: the results were quite satisfactory: 100% prevention of acute pyelonephritis, and 92% absence of symptomatic infections.

Conclusions: We have been able to confirm the high effectiveness of the product, the absence of adverse effects, an excellent acceptance by the parents and patients regarding a long-term treatment, and a very low rate of dropouts. Prospective double-blind randomized and placebo-controlled trials will be required to issue recommendations supported by a high degree of evidence.

PROANTHOCYANIDINS AMERICAN CRANBERRY EXTRACT AS AN ALTERNATIVE TO ANTIBIOTIC PROPHYLAXIS IN PEDIATRIC PATIENTS WITH LOWER URINARY TRACT MALFUNCTION.

Martin-Crespo RM, Carrera N., Ramirez H., Martinez Y., Luque Mialdea R.
to be published

Abstract

Introduction & Objectives: Low doses of antimicrobial prophylaxis remain being the recommended intervention in children at high risk for urinary tract infection (UTI), but at the expense of increased antimicrobial resistance. The objective is to evaluate the use of an American cranberry extract with a high concentration of proanthocyanidins (PAC) as an alternative to antibiotic prophylaxis in pediatric patients with recurrent urinary tract infections (UTI) and concomitant Lower Urinary Tract Malfunction (LUTM).

Material & Methods: Since 2010, 101 patients with LUTM and recurrent UTI have been treated with PAC (oral solution) as a substitute for antibiotic prophylaxis. 36 males and 65 females were included, from 12 months to 16 years old. Indications for PAC treatment were: dysfunctional voiding (31 cases); vesicoureteral reflux (VUR) (12); Neurogenic bladder (10); bladder pathology (10); vesicostomy due to severe LUTM (2); nephrectomy due to VUR nephropathy (4); urodynamic prophylaxis (22); anterior urethral valves (2); Urethritis (n=4); Non-obstructive megaureter (4). Our step-by-step treatment protocol of LUTM is based on urotherapy; standard urotherapy and specific intervention (biofeedback), with special emphasis on preventing post-void residual urine. Antibiotic was replaced by PAC after 6 months of starting LUTM treatment once residual urine became non-significant. Minimum duration of the LUTM treatment was 1 year.

Results: Only 2,97 % of patients (3 patients) suffered of episodes of UTI. One case has vesicostomy, one neurogenic bladder and the other dysfunctional voiding. Antibiotic prophylaxis was re-established in these patients. Pseudomonas aeruginosa was found in 2 patients and Escherichia coli in one. The adhesion to PAC treatment was 100% and no cases of adverse events, side effect or intolerance were reported.

Conclusions: A high PAC concentrated American cranberry extract has been easy to administrate by oral route in all our patients. PAC have proven that significantly prevent the UTI recurrence in our LUTM protocol reducing UTI incidence by 97.03% of patients as well as the antibiotic consumption in this pediatric population with a high risk of UTI. We propose a high PAC concentrated American cranberry as an alternative to replace the current nocturnal antibiotic prophylaxis in children at risk of UTI and concomitant treatment of LUTM to avoid significant post-void residual urine.
Abstract

Introduction: Proanthocyanidins (PAC) of American cranberry (AC) protects against urinary tract infections (ITU) caused by *Escherichia coli* (Ec) inhibiting their adhesion to the urothelium. This is a dose depending effect. Its use in children is not well known due to lack of publications on this subject.

Objective: to know the patients tolerability, efficacy and safety to a high PAC concentration of an AC (Cysticlean®, CYS),

Material & methods: 74 children ranged (6 months to 18 years), 53 girls and 21 boys diagnosed of Recurrent UTI by Ec and with the following pathologies: Ureter-bladder reflux, sphincter vesical dysfunction, Neuropathic bladder, Hypeactive bladder, Enuresis syndrome, Pyeloureteral stenosis, Megaureter and Ureterocele), were treated with 1 caps/sachet of CYS a day during 5,6 m (ranged 1 m – 1y).

Results: 79,4% of children preferred sachets than capsules, CYS treatment was well tolerated by 72 patients (97,3%). 2 patients rejected to be treated and were excluded from the study. 1 patient withdraw from the study due to a diarrhea episode. 90% of patients did not had a UTI during the treatment period, 6,6% of patients had less UTI than before to start CYS treatment and UTI infection rate did not change in 3,3% of patients. No adverse events/side effects related to CYS were reported. 91,3% of patients who finished the study continued their treatment with CYS. Re tolerability and treatment adhesion, 70,8% of patients took CYS daily, 25% half of the recommended dose and 4% less than a half of the recommended dose.

Conclusions: CYS was very effective to treat and prevent UTI in children. No side effects/adverse reactions related to CYS were reported and its tolerability was considered excellent because it was very well accepted by children.
Abstract

Introduction: Recurrent urinary infection (recurrent UTI) mainly caused by *Escherichia coli* (Ec), is a very frequent illness in women and use to be treated and prevented with antibiotics and sub-therapeutic doses of antibiotics respectively. Continuous use can accelerate the appearance of bacterial resistance to the most frequently-used antibiotics, forcing us to consider other complementary treatments for these patients. A high proanthocyanidins American cranberry extract Cysticlean® (CYS) has proven to be effective to prevent ITU recurrences in previous studies we have tried to re-evaluate whether CYS could be helpful to prevent recurrent UTI.

Material & methods: 92 females ranged 18 to 65 y old with a history of recurrent UTI and a urinary infection positive to Ec were included and treated with 1 capsule of CYS every day up to 3 months. Patients were visited at 3 weeks and 3 months after treatment started.

Results: 14 patients were excluded of the analysis due to lack of data and/or not adjusted to the inclusion/exclusion criteria. There were 7 UTI recorded between first 3 weeks of the follow up and 4 more between 3 weeks and 3 m. A highly significant reduction of UTI symptoms was reported through the study period. Total incidence of UTI was 14.1%, lower than 20% usually reported in other studies.

Conclusions: The 3-month long course of CYS in patients with recurrent infections was proven to be a well-tolerated treatment, showing a very low rate of re-infections compared to the previous reports. Further studies are needed to confirm these data.

Cysticlean®, A HIGHLY PAC STANDARDIZED CONTENT IN THE PREVENTION OF RECURRENT URINARY TRACT INFECTIONS: AN OBSERVATIONAL, PROSPECTIVE, COHORT STUDY.

Francisco Sánchez Ballester, Vicente Ruiz Vidal, Emilio López Alcina, Cristina Doménech Pérez, Eva Escudero Fontano, Ana María Oltra Benavente, Ana Montoliú García, Marco Andrés Sobrón Bustamente.

BMC Urology 2013, 13: 28
DOI:10.1186/1471-2490-13-28

Abstract

Background: the present study was aimed determining the prophylactic efficacy of American cranberry (AC) extract (Cysticlean®, CYS) in women with recurrent symptomatic post-coital urinary tract infection (PCUTI), non-consumer of AC extract in the past 3 months (m) before inclusion and to determine changes in their quality of life (QoL).

Material & methods: This is a single center observational prospective study in a total of 20 women (mean age: 35.2 years; half married). Patients were followed up to 6 m with a control at 3 m after 1st visit. Patients were recommended to take 1 capsule a day of CYS every day during the study. All patients should have PCUTI within 3 m prior to enter into the study.

Results: all patients had UTI with urinoculture positive to Ec. The number of PCUTI in the previous 3 m prior to start CYS treatment was 2.8 ±1.3 and it was reduced at 0.2±0.5 at month 6 (p<0.0001), which represents a 93% improving. Only 3 symptomatic UTI were recorded at the end of the 6 m treatment period. At baseline, the mean score on the VAS scale (range 0–100) to assess QoL was 62.4±19.1 and it increase to 78.2±12.4 at month 6, representing a 20% improvement (p<0.0002).

Conclusions: prophylaxis with American cranberry extract CYS could be an alternative to classical therapies with antibiotics. Further studies are needed to confirm results obtained in this pilot study.
Cysticlean® AND PROPHYLAXIS OF RECURRENT URINARY TRACT INFECTIONS: IS THE AGE A LIMITING FACTOR?

Authors: Fernando Rodríguez Escovar, Armando de Gracia Nieto, Juan Manuel Villamizar Avendaño. Revista Médica Electrónica Portales médicos.com ISSN 1886-8924

Abstract

Background: urinary tract infections (UTI) in women are quite common among women at fertile and post-menopausal age. 2 recent studies have shown the efficacy of Cysticlean® (CYS) to prevent UTI recurrences in women from 18 to 65 y old. We have evaluated whether it was any difference on women related to fertile/non-fertile status.

Material & methods: 161 women from 2 identical observational studies of women with recurrent UTI treated with CYS, who finished the 3 months (m) treatment according to the protocol, were divided in 2 groups: group A included patients between 50 to 60 years (y) and group B included patients between 18 to 49 y. Infection rate and symptoms were compared between groups.

Results: no significant differences were found between groups A and B re reinfection rate at 3 weeks of CYS treatment (A=9,1%; B=10,6%) and at 3 m (A=11,8%;B=5,9%). Symptoms were more frequent in group B but only microhematuria was statistically significantly higher in this group compare to group A (p<0,05). Number of patients without reinfection at 3 m treated with CYS was similar in both groups.

Conclusions: recurrent UTI prophylaxis with CYS daily up to 3 m in women was not affected by age.

CLINICAL EVALUATION OF A CRANBERRY EXTRACT IN THE TREATMENT OF RECURRENT CYSTITIS IN PATIENTS OVER 70 Y OLD. THE GERHOGAR Cysticlean® STUDY. A PROSPECTIVE OBSERVATIONAL STUDY.

Authors: Jesús-José Cuadrado Blanco MD, Guzmán Tamame González. MD, PhD., Agapito Gómez Villa MD, Amparo del Cañizo. MD, Juan F. Macías Núñez MD, PhD.

Submitted

Abstract

Background: uncomplicates cystitis (UC) and antibiotic resistance (AR) are a public health worldwide. Alternative treatments should be evaluated to reduce UC incidence and antibiotic consumption. Cysticlean® (CYS) a cranberry extract clinically tested has been used instead of antibiotics to treat UC in patients over 70 years (y) old.

OBJECTIVE: to evaluate whether CYS could be an alternative to antibiotics to treat UC.

Material & Methods: 160 ambulatory patients (p) ranged 70 to 104 years (y) old with recurrent UC confirmed by a positive urinoculture to Escherichia coli (Ec) and 2 or more sings/symptoms were treated with 2 capsules of CYS bid and follow up to 10 months (m).

Results: 31 of 38 patients of the group 1 treated for 1 m were successfully treated with CYS and 100 patients of 122 of the group 2 were successfully treated and followed up to 10 m. (81,57% and 81,96% respectively). Low glomerular filtration rate and high HUGE score suggest higher risk of re-infection in females than males No side effects/adverse reactions were reported.

Conclusions: CYS is an alternative to antibiotics to treat and prevent UC recurrences caused by Ec. CYS may offer a way of reducing the growing problem of antibiotic resistance.
Abstract

Objective: to evaluate whether a high concentration proanthocyanidins cranberry extract (Cysticlean®) could significantly reduce the incidence of urinary tract infections in a population younger than 70 years old.

Material & methods: 27 patients diagnosed of recurrent urinary tract infection (7 men) were required to stop taking any antibiotic to treat/prevent their urinary infections and started to be treated with a 240 mg of proanthocyanidins cranberry extract 1 capsule every 12 hours up to 1 year. Demographic and renal function parameters were evaluated as well as the urinary re-infection rate. Patients over 60 years were evaluated on their physical activity, psychological status, functional and social status (Geriatric evaluation).

Results: 21 patients (78%) did not have any urinary infection along the study period. 4 males and 2 females had one. Neither non-infected patients nor infected patients showed any significant difference on its Glomerular Filtration rate, Blood Creatinine, Blood urea and Huge before and after the treatment. No side effects/adverse reactions were reported.

Conclusions: 240 mg of a high proanthocyanidins concentrated cranberry extract 2 capsules a day has proven to significantly reduce the incidence of urinary infections in these patients without safety issues related to the extract. No changes were found on their renal function parameters and in their Geriatric evaluation.