Studying the role of sodium Aescinate (Reparildragees) in treatment of Mastalgia

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Abstract

Objectives: To evaluate the effect of Aescinate on the mastalgia patients of benign causes as a synergistic drug with other treatments of modalities.

Methods: Female patients (aged 9 to 75 years) with history of benign caused mastalgia (n=517) visited the Imam Ali hospital breast clinic, Baghdad, Iraq, between January 2014 and January 2019, were included. Those who met to the study criteria; 400 patients completed the study, were prospectively divided into those who had cyclical mastalgia (n=200) and those who didn’t (n=200), then subdivided into five subgroups (each n=40). For all patients, we evaluated the history of trauma, diet and lifestyle (wearing bra, sleeping prone, drinking caffeine containing drinks, fatty foods), breast size, history of breast infections, hormonal assay, radiological assessment (ultrasound and/or mammography), pain severity/response charts and histopathological test pre and post-treatment. The observation follow-up were made at study initiation and accordingly (2 weeks-2 months) visits and at least to 6 months total period with at least 2 menstrual periods within.

Results: The Aescinate (Reparildragees) synergistically treated mastalgia with danazol groups showed a significant reduction in pain charts response 80% for cyclical type and 67.5% for non-cyclical compared to groups not, while for evening primrose oil groups were 70% and 60% respectively. Also for histopathological response which was best for periductal cyclical mastitis for danazol and evening primrose oil with Reparilgroups (77% and 67% respectively) as do nipple discharge (63% and 28% respectively) over the study period. The cyclical group show more response than noncyclical group for mastalgia, histopathological and nipple discharge after treatment with synergistic Reparildragees.

Conclusion: Aescinate (Reparildragees) improve danazol and evening primrose treatment regimens of mastalgia of benign cause’s response.

Key words: Aescinate, Reparildragees, cyclical mastalgia, non-cyclical mastalgia

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Introduction

Medical knowledge is ever changing. As new research and clinical experience broaden our knowledge changes in the treatment and therapy may be required by adding, synergizing and combining new drugs.

There are many findings that suggest a constellation of many causative and assisting factors rather than a single domineering mechanism, likely mediating female breast pain (mastalgia) with contributing factors varying according to the type of mastalgia. Nevertheless all treatment regimen modalities, life style change instructions and supportive measures coincide in one common positive effect leading to the mastalgia resolution by identifying operative the theories

of mechanism of action of these treatment regimens, it is reasonable to speculate that single modality and/or drug can’t
gave us the best response. Increasing knowledge about the mechanisms of mastalgia and drugs actions lead us to the new
era of treatment advance.

Reparildrages contain the active component Aescin, which is the main component of Aesculus hippocastanum
(Hippocastanaceae) the horse chestnut tree extract; it manifests an obvious clue for a significant clinical activity in chronic
venous insufficiency (CVI), post-oedema and haemorrhoids. In one controlled trial compression therapy, aescin had the
same effect as treatment for CVI as other medical treatments (such as breast cancer treatment). The therapeutic benefit is
well established by different animal models trials, proving with no doubt the anti-oedematous, anti-inflammatory and
venotonic properties, mainly related to the molecular mechanism of the agent, allowing improved entry of ions into
channels, thus raising venous tension in both in vitro and in vivo conditions. Other mechanisms including PGF (2) release
from veins, 5-HT antagonism, histamine and decrease mucopolysaccharides catabolism had underlined the wide
mechanisms of theaeascin therapeutic activity. The excellent clinical tolerability of aescin and its benefits in patients with
CVI, haemorrhoids and peripheral oedema formation.[1]

Historically, the seed extract was used for hyperpyrexia, rheumatism, bladder and gastrointestinal disorders,
hemorrhoids (as early as 1886), leg cramps, post-operative edema, and topically for clearing skin conditions. Currently,
horse chestnut seed extract (HCSE) is widely used in Europe for chronic venous insufficiency. In the United States,
HCSE had accepted a wide range of effective appliance as a therapy for CVI and edema, based on two decades of
numerous randomized controlled trials in prominent, peer-reviewed journals. [2,3 and 4]

Mechanism of action of aescin is:

Anti-edematous by increasing sensitization to calcium ions, decreases permeability of small vessels and veins
enhancing contractile activity, leading to improve venous tone with a “sealing effect” at the injury zones with a final
outcome of decreased edema and swelling.[5, 6]

The anti-edematous properties of aescin contributed in part to its inhibition of hypoxia and the resultant
reduction of ATP content in endothelial cells initiating the release of mediators like prostaglandins, platelet activating
factor with neutrophils chemotaxis leading to venous stasis and edema. Aescin also reduces the adherence and activation
of white blood cells inhibiting edema and protecting the vessels. [7, 8 and 9]

Anti-inflammatory properties of aescin by interfering release of inflammatory mediators by decreasing leukocyte
activation and adhesiveness had been demonstrated in animal models. In a rat model of pleurisy, aescin administration
decreased leukocyte migration into the pleural cavity and inhibited the release of inflammatory mediators.[9]

Venotonic properties aescin increased venous tone by 10-20 percent at low concentrations (oral dosing) in
humans.

Clinical Indications for aescin are for chronic Venous Insufficiency, varicose veins, venous stasis ulcers, post-
operative edema, hemorrhoids, inner ear perfusion and ureteric stones. [1]

There are few relatively known side Effects and Toxicity HCSE and is generally considered to be safe when
given at recommended dosages. Preclinical studies on the safety of HCSE showed no oral toxicity or mutagenic or
teratogenic activity. [10]

In clinical trials for CVI published to date, the rate of adverse events associated with HCSE (horse chestnut
seed extract) administration is 0.9-3.0 percent, comparable to placebo. The gastrointestinal side effects and dizziness are
more often associated with high doses of HCSE. In the case of topically applied aescin, rare incidences of acute
anaphylactic reaction have been reported. Lesser skin sensitivities to topical HCSE are characterized by redness and
itching at the site of application. [3, 11]

Mastalgia (breast pain) comprises one of the most common presentations to the breast disorders clinics around
the world; it also comprises a wide range of causes from normal cyclical pain to malignancy causes. The vast majority of
causes are benign although it is not uncommon that malignancy can present with breast pain, without a distinct breast
mass. About 7 in 10 women can develop breast pain at some stage in their lives. Mastalgia can be roughly discriminated
into two types which are cyclical and non-cyclical; overall, 92% of patients with cyclical mastalgia and 64% with
noncyclical mastalgia (NCM) can get rid of mastalgia with judicious therapies. [12]
The cyclical mastalgia which appears 2 or 3 days before the start of menses periods, in about 2 in 3 women the pain develops in the days just before a period, it can occur at any age after menarche commonly between the 30 and 50 years age, prediction that women with cyclical mastalgia have more hormonal changes sensitivity of the glandular breast tissues than usual. It is not a disease of any hormone or due to problem in the breast itself as evidenced by relief in postmenopausal women. It may be associated with periductal mastitis/ductal ectasia or/and fibroadenosis/fibrocystic disease.

While in the remainder the pain is not related to periods - non-cyclical and usually affects women above 40, noncyclical breast pain is often related to internal anatomical changes, such as a repeated minor traumas, infections, periductal mastitis/ductal ectasia or/and fibroadenosis/fibrocystic disease. [13-17]

<table>
<thead>
<tr>
<th>Breast pain characteristics</th>
<th>Cyclic breast pain</th>
<th>Noncyclic breast pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual cycle related</td>
<td>Described as heaviness, aching ordull</td>
<td>Unrelated to the menstrual cycle</td>
</tr>
<tr>
<td>Often with lumpiness and/or breast swelling</td>
<td>May be associated with breast swelling</td>
<td></td>
</tr>
<tr>
<td>The upper outer portions of both breast usually affected and can radiate to the underarm</td>
<td>Usually single breast with localization, but may be diffusing across the breast</td>
<td></td>
</tr>
<tr>
<td>Escalating in intensity 10 days before menses and then eases up afterward</td>
<td>Constant or alternating pain</td>
<td></td>
</tr>
<tr>
<td>Women in their 20s and 30s are most affected as well as women in their 40s who are transitioning to menopause</td>
<td>Affect women after menopause mostly</td>
<td></td>
</tr>
</tbody>
</table>

There are various evidenced mechanisms of mastalgia like:

- Endocrine Abnormalities theoretically increased ovarian estrogen secretion with or without progesterone production deficiency, thyroid dysfunction and hyperprolactinemia are the main players.

The studies of serum hormones levels do not support this theory, as hormonal levels were found to be similar in patients and controls except for hyperprolactinemia.

A study by Peters et al. clears that mastalgia patients had a significantly greater rise in prolactin compared with the controls supported by a study at Cardiff Mastalgia Clinic who reported the same. [18-23]

- Pain with unknown cause coming from the breast tissue itself in the absence of any lumps, tumors, or other abnormality being detected.

- Radiating chest wall pain, under the breast rather than the breast itself, may be of muscular or bony origin accounts for some cases. Another cause may be that large sized breasts women due to obesity or inheritance may induce noncyclic breast pain due to Cooper's ligaments stretching, which are bands of connective tissue that support and shape breast tissue. Neck, shoulder and back pain may accompany breast pain due to large breasts.

- Tea, coffee, chocolate, energy-drinks, smoking and salty fatty foods.

- Infection is a cause in a small number of cases.

- Breast cancer is a very uncommon cause of breast pain.

- Breast structure. Noncyclic breast pain often results from changes that occur in the milk ducts or milk glands. This can result in the development of breast cysts and periductal mastitis. Breast with repeated minor trauma, unsupported breast, wrong sleeping positions compressing the breast especially in prone position, previous breast surgery and other localized breast factors can lead to breast pain.
• Organ radiating pain from muscles, joints, esophageogastric, gallbladder, lungs or heart may radiate to the breast.

• Alternating sensitivity of breast tissue to circulating hormones due to imbalance of fatty acids within the cells may play a role.

Separately or in combination provoking the pain, all the above may cause mastalgia. [16-21]

The pain is often mild but in some women its more severe, or for the times it may flare up worse than usual affecting life quality but if it is mild, then no treatment needed with reassurance that cyclical or non-cyclical breast pain is not a symptom of cancer or serious breast disease or even it is not related to breast as pain settles by itself within 3-6 months, but can come back from time to time.[20]

Pain evaluation: There are some tests to evaluate the condition which may include the following:

• Clinical breast examine for changes in breasts and the lymph nodes in axilla and lower neck. If medical history and physical examination of chest and abdomen organs to determine whether the pain could be related to another conditions reveal nothing then additional tests may be requested.

• Mammogram. If a breast lump or unusual thickening, or a focused area of pain in breast tissue and for 40 years and above then diagnostic mammogram must be done.

• Ultrasound. To evaluate a focused area of pain even if the mammogram appears normal.

• Breast biopsy. Suspicious breast lumps, areas of thickening or unusual areas seen during imaging exams may be require to a diagnosis. [12, 13, 16, 17, 18 and 20]

Obviously, the best treatment for breast pain depends on what is causing it.

For many women, breast pain resolves on its own over time but if needed these steps must be done including the following:

• Underlying or aggravating factors manipulation. This may be done by simple adjustments with supporting bra when you have pain or even 24 hours a day for the week before a period is helpful with avoidance of underwired bras. Wear a sports bra when you exercise and in sleeping time with changes in sleeping positions especially prone one may help.

• Painkillers such as paracetamol or ibuprofen when the breasts are painful.

• Topical appliance of anti-inflammatory medications such as topical diclofenac, ibuprofen or others as their side-effects are very rare.

• Stop drinking or eating caffeine containing beverages and foods. This has not been proven in research studies. However, in the week or so before a period it may be worth trying to cut out tea, coffee and cola which contain caffeine to see if this helps.

• Consider stopping medications. Cessation of contraceptive pill or hormone replacement therapy (HRT) may make cyclical breast pain better with switching birth control methods may help breast pain symptoms.

• Diet conflict. Adjusting diet by reducing animal fatty acids (such as butter, cream and fatty meat) as they have theoretical mastalgia role, and increasing intake of fresh vegetables and fruits with decreasing salt can be helpful. [24]

• Try Vitamin E. Studies have not consistently shown benefits of vitamin E for treating breast pain, though some women find it helpful. [25, 26]

• Try Omega–3 fatty acid. Though not yet hard base proven, increased intake of fish oils/omega-3 supplements helpful for some women.
Evening primrose oil (EPRO) is often recommended as a treatment for breast pain. A 6 weeks is required before benefit can be assessed with a 1-2gms/day dose given for improvement in severity of cyclical and non-cyclical mastalgia. If symptoms improve, continue these tablets. [27]

Drugs to block hormones. Medication such as tamoxifen or danazol can ease pain in most cases by reducing or blocking the effect of estrogen and other hormones. Bromocriptine blocks prolactin in the hypothalamus is used when there is hyperprolactinemia. However, significant side-effects are common with these drugs restricting their use so not usually tried unless severe pain which occurs during most months and does not ease with other treatments.[28-31]

Aescin (Reparildragees) may inform to these medications for its properties as mentioned above as synergistic medication to help get a better response for mastalgia.

By understanding the suspected causative mechanism of mastalgia and applying the effects of aescin, it may play a major adjuvant role in the management of mastalgia.

Patients and methods

This prospective longitudinal study was conducted in Imam Ali general hospital breast clinic in Al-Sadder city, Baghdad, Iraq, during January 2014 and January 2019 were female patients suffering from mastalgia who came or were referred to our breast unit for management.

Five group clinical trials of 517 patients with breast pain from all ages were included in this study, but only 400 matches the study design criteria.

Disease history including geodemographic information, clinical and radiologically (ultrasound and mammography for those above 40 years) assessment of the patients clinical condition were done. After overall assessment a decision was made by authorized surgeon to exclude patients according to the causative underlying disease, the exclusion details were those who had trauma, pregnancy, lactation related problems, lumps related pain and carcinoma, after exclusion only 517 patients fit the designed criteria. But only 400 commit to the follow-up due to multi-causes of death, pregnancy, changing of breast clinic due to change of address or travelling and due to socio-economic purposes.

All patients were divided into two groups (200 each) according to the pain relation to the monthly period (menstrual), those are cyclical and non-cyclical groups and re-division to subgroups was made to five subgroups (40 each) according to treatment modalities by regular random selection. [20, 29 and 31]

Those subgroups were:

1. Patients prescribed with danazol capsule 200mg once at night with Reparildragees 2 tablet twice daily.
2. Patients prescribed with danazol capsule 200mg once at night only.
3. Patients prescribed with evening primrose oil (EPRO) capsule 1000mg once twice daily with Reparildragees 2 tablet twice daily.
4. Patients prescribed with evening primrose oil (EPRO) capsule 1000mg once twice daily.
5. Patients prescribed with Reparildragees 2 tablet twice daily.

All patients were reviewed within intervals of 2 weeks to 2 months period visits to the breast clinic and a follow up period of 6 months with at least 2 menstrual cycles within this follow up period to decrease bias of treatment modality response.

Ethical consideration of proposal of research was approved by the scientific and ethical comity in the Al-Resafa general directorate/Al-Imam Ali general hospital. Agreement of scientific committee in Al-Imam Ali general hospital and health authority in the hospital was taken before starting the study, as do foundation of the study by the breast disease program unit in the Iraqi ministry of health.
A written consent was taken from each included patient after full explanation of the aim of the study and insuring the patients about the confidentiality of the collected data telling the patients that this data will be anonymous and will not be used but for the research purposes and no name will be revealed.

A pain chart was designed with an additional questioner paper consisting of the following questions with the collaboration of the Iraqi breast diseases clinic guidelines for non-cancer patients:[14, 32]

• Where in your breast do you feel pain?
• How long have you had breast pain?
• On a 10-point scale, how severe is your pain?
• Do you have pain in one or both breasts?
• Does the pain seem to occur in any sort of pattern?
• Do you have other nipple discharge?
• Have you noticed any skin changes, such as redness or a rash?
• Have you recently experienced a pregnancy loss or termination?
• How does the pain impact your quality of life, sleep, sexual activity or work?
• Does your pain make you less able to perform daily activities?

All patients in this study were subjected to trucut biopsy at the site of maximum pain (trigger point) marked by palpation and then authenticated by a photograph and during the follow up period by applying pressure to the area to see if it reproduce pain, re-doing the trucut biopsy at the end of the follow up period was taken from the photo-marked area to evaluate the pathological response. [33]

All patients in this study were given the same instruction to help mastalgia management like: [20, 29, 31, 34-36]

1. Well supporting bra 24 hours a day and a sports bra when exercise and in sleeping time also change sleeping positions especially prone one.
2. Cut out tea, coffee and cola, other beverages which contain caffeine and smoking.
3. Adjusting diet by reducing animal fats and increasing intake of fresh fruit, vegetables, water and fluids with decreasing salt.
4. Stop contraceptive pill or hormone replacement therapy (HRT) and try other non-hormonal adjustments of birth control.
5. Psychological reassurance.

**Response assessment**

This was done for the patients and pain response was classified into 4 groups which are:[20,29,31,37,38]

I. An excellent response leaving no residual pain.
II. Substantial response leaving some residual pain but considered by the patient to be easily bearable.
III. A poor response leaving substantial residual pain that can’t be bearable by the patient.
IV. No response.

Estimation of the responses were during the follow-up period of 6 months with at least 2 menstrual periods by visits of 2 weeks to 2 months periods according to the pain chart designed and the patient were considered to have a response if they were class I and II. [39]

Statistical analysis was made for the collected data and introduced into Microsoft excel sheet and loaded into IDM-SPSS V24. Descriptive statistics were presented by using means ±SD and frequency distribution tables with graphs while paired sample T-test was used to find out the significance of statistical difference between means of measured variables at pre and post-operative times, P value <0.05 was considered as cutoff point crimination of significance.

**Results**

A total of 517 patients with mastalgia were included in this study, 117 patients were lost: 3 died, 31 due to socio-economic factors, 35 get pregnant and 48 changing their breast clinic due to change of residency (according to the roles of the Iraqi health ministry regulations). Four hundred patients were included with final results.

The age groups were from 9 to 75 years old with a mean of 34±20 years, those 400 patients were divided into 2 groups, 200 each with subdivision into 5 subgroups of 40 patients each according to the clinical trial with the response to it, table 1.

Table 1: Distribution of studied groups (40 patients each) according to the type of clinical trial and response to the treatment trial according to pain chart.

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Cyclical mastalgia No. (%)</th>
<th>Non-cyclical mastalgia No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danazol+Reparildragees</td>
<td>32 (80)</td>
<td>27 (67.5)</td>
</tr>
<tr>
<td>Danazol</td>
<td>25 (62.5)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>EPRO*+ Reparildragees</td>
<td>28 (70)</td>
<td>24 (60)</td>
</tr>
<tr>
<td>EPRO*</td>
<td>21 (52.5)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>Reparildragees</td>
<td>20 (50)</td>
<td>19 (47.5)</td>
</tr>
</tbody>
</table>

*EPRO=Evening Prim Rose Oil

Percentage of each group and subgroup are clarified in the tables and overall response for each group as well.

The pathological response by a trucut biopsy of the pain triggering sites pre-and post-treatment results showed that the periductal mastitis and duct ectasia with fibrocystic class and nipple discharge as do reduced post-treatment as shown in table 2,3,4 and 5.

For nipple discharge it is either spontaneous or by squeezing considered positive, while for histopathological response it is positive if it’s of moderate and severe degrees of periductal mastitis and ductal dilatation and same for fibrocystic class.

Table 2: Histopathological and nipple discharge of mastalgia pre-treatment according to treatment modality of cyclical mastalgia (40 patients each).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Nipple discharge</th>
<th>Fibrocystic class</th>
<th>Periductal mastitis No.</th>
<th>Duct ectasia</th>
</tr>
</thead>
</table>

Table 3: Histopathological and nipple discharge of mastalgia post-treatment according to treatment modality of cyclical mastalgia how remain having positive finding.

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Nipple discharge</th>
<th>Fibrocystic class</th>
<th>Periductal mastitis</th>
<th>Duct ectasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>D+R</td>
<td>30 (75)</td>
<td>32 (80)</td>
<td>26 (65)</td>
<td>28 (70)</td>
</tr>
<tr>
<td>D</td>
<td>28 (70)</td>
<td>30 (75)</td>
<td>29 (72.5)</td>
<td>27 (67.5)</td>
</tr>
<tr>
<td>EPRO+R</td>
<td>32 (80)</td>
<td>30 (75)</td>
<td>28 (70)</td>
<td>28 (70)</td>
</tr>
<tr>
<td>EPRO</td>
<td>31 (77.5)</td>
<td>29 (72.5)</td>
<td>30 (80)</td>
<td>29 (72.5)</td>
</tr>
<tr>
<td>R</td>
<td>30 (75)</td>
<td>29 (72.5)</td>
<td>27 (67.5)</td>
<td>28 (70)</td>
</tr>
</tbody>
</table>

D=Danazol, R=Reparil, EPRO=Evening prim rose oil.

Table 4: Histopathological and nipple discharge of mastalgia pre-treatment according to treatment modality of non-cyclical mastalgia (40 patient each).

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Nipple discharge</th>
<th>Fibrocystic class</th>
<th>Periductal mastitis</th>
<th>Duct ectasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>D+R</td>
<td>28 (70)</td>
<td>26 (65)</td>
<td>27 (67.5)</td>
<td>23 (57.5)</td>
</tr>
<tr>
<td>D</td>
<td>26 (65)</td>
<td>24 (60)</td>
<td>28 (70)</td>
<td>25 (62.5)</td>
</tr>
<tr>
<td>EPRO+R</td>
<td>25 (62.5)</td>
<td>28 (70)</td>
<td>29 (72.5)</td>
<td>26 (65)</td>
</tr>
<tr>
<td>EPRO</td>
<td>26 (65)</td>
<td>27 (67.5)</td>
<td>27 (67.5)</td>
<td>29 (72.5)</td>
</tr>
<tr>
<td>R</td>
<td>27 (67.5)</td>
<td>26 (65)</td>
<td>26 (65)</td>
<td>28 (70)</td>
</tr>
</tbody>
</table>

D=Danazol, R=Reparil, EPRO=Evening prim rose oil.

Table 5: Histopathological and nipple discharge of mastalgia post-treatment according to treatment modality of non-cyclical mastalgia how remain having positive finding.

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Nipple discharge</th>
<th>Fibrocystic class</th>
<th>Periductal mastitis</th>
<th>Duct ectasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>D+R</td>
<td>16 (57.1)</td>
<td>14 (53.8)</td>
<td>12 (44.4)</td>
<td>12 (52.1)</td>
</tr>
<tr>
<td>D</td>
<td>19 (73)</td>
<td>20 (83.3)</td>
<td>17 (60.7)</td>
<td>17 (68)</td>
</tr>
<tr>
<td>EPRO+R</td>
<td>18 (72)</td>
<td>15 (53.5)</td>
<td>13 (44.8)</td>
<td>14 (53.8)</td>
</tr>
<tr>
<td>EPRO</td>
<td>20 (76.9)</td>
<td>19 (70.3)</td>
<td>20 (74)</td>
<td>19 (65.5)</td>
</tr>
<tr>
<td>R</td>
<td>21 (77.8)</td>
<td>20 (76.9)</td>
<td>20 (76.9)</td>
<td>19 (67.8)</td>
</tr>
</tbody>
</table>

D=Danazol, R=Reparil, EPRO=Evening prim rose oil.

Histopathological and nipple discharge of mastalgia post-treatment percentage was for cyclical and non-cyclical type for treatment modality with Reparil was as shown in table 6.

Table 6: Best response % of histopathological and nipple discharge of mastalgia post-treatment for Reparil added treatment modalities.

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Nipple discharge (%)</th>
<th>Fibrocystic class (%)</th>
<th>Periductal mastitis (%)</th>
<th>Duct ectasia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>63.3</td>
<td>42.9</td>
<td>62.5</td>
<td>46.2</td>
</tr>
<tr>
<td>NC</td>
<td>55.6</td>
<td>57.2</td>
<td>47.9</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

The results of this prospective longitudinal study showed that mastalgia response in our study is lower (80%) than that of Millet and Dirbas review of breast pain management which was 92% of patients with cyclical mastalgia and about the same (67.5%) for non-cyclical mastalgia which is 64% in that study who can obtain relief of their pain with the best judicious use of several available therapies.[12]

Aescin (Reparildragees) by its biological effects on the tissues plays important roles to decrease periductal mastitis/ductal ectasia by its anti-edematous, anti-inflammatory, venotonic and other mechanisms, i.e. release of PGF(2) from veins, antagonism to 5-HT and histamine, reduced catabolism of tissue mucopolysaccharides and improves circulation which promote healing.[1]

Further underline the wide ranging mechanisms of the therapeutic activity of aescin, it play a synergistic role in the mastalgia management with NSAIDs and main treatments (danazol/EPRO) with diet and life style changes.

It is for the first time that aescin (Reparildragees) used for the mastalgia management, as there were no such study done before.

The histopathological findings were better for cyclical than for non-cyclical type of mastalgia and Reparil added danazol better than EPRO added Reparil for all (nipple discharge, fibrocystic, periductal mastitis and duct ectasia.

Best response was for periductal mastitis for treatment with D+R as it was 77% while for EPRO+R treatment was 67.9%, this can be attributed to the effects of Reparil on tissues and thereby improve mastalgia response to drugs. [5-9]

No similar Studies on human female breast were done, but multiple human studies of patients with postoperative circulation, renal stones, chronic venous insufficiency, ear disturbances and others were done and it is now recommended in their management. Ahuman study of patients with chronic venous insufficiency, showed 5 mg aescin given intravenously twice daily fora week resulted in a 33-percent reduction of leukocytedeficiency, a 50-percent decrease in macrophage numbers, and a 46-percent increase in neutrophils in inflammatory exudates. [41]

Also animal studies in dogs and in vitro studies using human saphenous veins demonstrated Aescin’s venotonic properties are linked to its ability to enhance production of prostaglandin F2 which inhibits venous tissue mucopolysaccharides catabolism and improves venous contractility. [3] One of these studies was on dogs with an injectable aescin dose of 25-50 mg resulting in a 21% increase in venous pressure and an increase in final maximum pressure of 30 percent compared to baseline. [13]

In the in vitro human saphenous veins studies with purified aescin dose-response curve reveals an increased venous tone by 10-20% at low concentrations that would correspond to reasonable oral dosing in humans. [42]

Two clinical trials demonstrate HCSE given intravenously decreases skin temperature and edema in postsurgical patients, first trial was for patients undergoing surgery for hernia repair, meniscus removal or lower leg fractures receiving 5-10 mg aescin intravenously twice daily starting at day prior to and three days after surgery with skin temperature comparison between the surgical area and the contralateral side as it is a relevant indicator of circulation and swelling in the affected area and it also shows that it was lower in the operated side than in the post-surgical patients receiving no treatment. [43]

In the second trial, hand surgery patients received 10 mg intravenous aescin twice daily were assessed with infrared thermography between treated side and contralateral side until symptoms disappeared with peak hand temperature difference which was noted on the second post-operative day, indicating improvement in skin circulation and swelling, compared non-treated group for whom peak hand temperature difference was not observed until four days post-surgery.[44]

In addition, these two clinical trials, numerous open-label studies have been published (in German and French) exploring the use of aescin, some with oral dosing. Overall, more than 1,200 surgical patients (having various major
surgeries) were involved, and most studies cited report therapeutic benefit from aescin treatment in the form of decreased edema. English full text of these published studies was not available for evaluation.[45]

Another interesting study was based on Aescin’s anti-inflammatory and venotonic properties and the vasoprotective antioxidant properties of troxerutin, a natural flavonoid derivative, and researchers investigated whether the combination of the two would have an effect on treating inner ear disturbances known to be due to circulatory insufficiency in the inner ear. Siegers et al administered 25 mg aescin and 450 mg troxerutin orally five times daily for approximately six weeks. The control group received 600 mg pentoxifylline (a drug that improves blood flow, blood rheology, and inhibits inflammation) daily, subjects receiving aescin/troxerutin group 68% experienced greater than 10 dB hearing improvement, seven of which improved by more than 14 dB from baseline while control group (pentoxifylline) only 18% improved more than 10 dB. Both medications were well tolerated without major adverse events.[46]

Finally, all studies using the aescin (Reparildragees) were advantaging from its anti-inflammatory, anti-edematous and Venotonic properties as adjuvant to other main treatments which all improve circulation.

In this study periductal mastitis was the second most common histopathological finding which depend on inflammatory reaction which also may be due to rupture of periductal cyst that ignite the inflammatory reaction with glandular and supportive tissues affection that produce many changes , one of which is pain. [47]

Conclusion:

Overall contradicting evidence exist on the role of aescin in the treatment of mastalgia but it is likely playing only a marginal role that needs additional delineation with encouraging evidence of mastalgia response modulation in this study, but needing further dislucidation in human studies getting use of its synergizing effects in multiple disease related treatment regimens making usefulness of its properties.

References