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# Comparison of Efficacy of Mometasone Furoate Cream with Betamethasone Valerate Cream in Reducing Acute Radiation Dermatitis in Head and Neck Cancer Patients Attending Rural Cancer Hospital in India

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**Abstract**

**AIM**

To assess and compare efficacy and safety of topical mometasone with betamethasone in acute radiation dermatitis (ARD) in patients undergoing radiotherapy for head and neck squamous cell carcinoma (HNSCC).

**MATERIALS AND METHODS**

This was a prospective, comparative, open-label, randomized controlled trial conducted at Viswabharathi Cancer Hospital, Kurnool. Participants were adults diagnosed with HNSCC and treated with 5 – 8 MV photon energy by linear accelerator. Test drug was applied daily on the irradiated area and allowed to remain for ~18 hours. ARD was assessed weekly during radiotherapy and for two weeks after radiotherapy. ARD assessment included pain, itching and Radiation Therapy Oncology Group (RTOG) scores.

**FINDINGS**

123 patients of HNSCC were recruited from February 2019 to January 2020 for this study. Patients were randomized into two groups – mometasone or betamethasone. In mometasone group, more no. of patients had their RTOG scores reduced to 1 {39 (62.90 %) vs 18 (29.51 %)}. While in betamethasone group, more no of patients had their RTOG scores reduced to 2 {15 (24.19 %) vs 39 (63.93 %)}. This difference in reducing RTOG scores was statistically significant ($p < 0.05$). Pain reduction and itch reduction were more in mometasone [{58 (93.55 %) vs 42 (68.85 %)} and {59 (95.16 %) vs 47 (77.05 %)} respectively]. Both treatments were effective when radiotherapy dose was < 6000 cGy ($p < 0.001$).

**CONCLUSION**

Mometasone local application after radiotherapy is efficacious and better than betamethasone in controlling ARD especially when skin dose is < 6000 cGy.

**Keywords**: Betamethasone, mometasone, radiation dermatitis, head and neck cancer, radiotherapy

## Introduction

Radiotherapy has become an essential component in multidisciplinary management of cancer in modern oncology. Inflammation in subcutaneous and vascular tissues occurring due to radiotherapy is called radiation dermatitis.[1] Among 95% of patients who receive anti-cancer radiotherapy, radiation dermatitis is one of the most common adverse effect seen in them.[2] ARD is defined as dermatitis or any

skin changes that occur within 2–3 weeks of initiating radiotherapy and continues 3–4 weeks after completion of radiotherapy, irrespective of dose and number of treatment cycles.[5] Studies have found that ARD occurs because of damage to tissues structurally, production of free radicals which have short half-lives, permanent damage to double-stranded DNA of nucleus and mitochondria, and inflammation of dermis and epidermis [6]. Acute ARD often manifests as blistering of skin and wet desquamation[7]. Dry desquamation presents as scaling and pruritus. It generally appears 3–4 weeks after radiation. Moist desquamation occurs due to the eradication of basal stem cells. This leads to serous discharge and exposure of the dermis beneath. Moist desquamation occurs four weeks after radiation.[8]

ARD is commonly seen in patients with head and neck cancer and lung cancer. Since these cases are treated with higher doses of radiation.[9] Adverse effects of radiation are associated with overproduction of prostaglandins, leukotrienes, prostacyclin and thromboxanes.[10] Corticosteroids are established drugs to suppress the synthesis of these eicosanoids by inhibiting key enzyme phospholipase A2.

Topical medication is generally prescribed when there is erythema or dry desquamation. Sucralfate or hyaluronic acid are often prescribed for a soothing effect.[11] Other topical medications having ingredients like Aloe vera gel, panthenol, almond oil, or chamomile oil are also prescribed and they have also been used with have shown variable outcomes.[7,12]

Topical steroids have established themselves as linchpins in reatment of various dermatological inflammatory conditions. The advent of hydrocortisone was followed by modification of its ring structure and side chains leading to the development of new steroid drugs, each having different potency towards inflammation and different adverse effects.[13] Topical steroids are known to cause local side effects like skin atrophy, telangiectasia, striae, rosacea, dermatitis around the mouth, skin infections and they also cause systemic side effects like HPA axis suppression.[1,14] Exact mechanism of anti-inflammatory action of corticosteroids is not clearly understood. However, it has been established that corticosteroids attach to their specific steroid receptors located in the cytoplasm and form a steroid-receptor complex. This complex migrates to the nucleus of the cell where it attaches to corticosteroid response elements (CRE). CRE is situated on promotor region of target genes. Stimulation of these CRE's leads to modification of gene expression, resulting in production of anti-inflammatory substances along with suppression of production of inflammatory mediators.[15] Chen et al demonstrated increased production of cytokines like IL-1B, TNF-α, TGF-β1 and IL-6 in murine skin when radiation of 15Gy was applied. These cytokines are responsible for ARD. Chen et al demonstrated a significant reduction in these cytokine levels when topical mometasone was applied.[16] Beetz et al. demonstrated a rise in IL-6 upon irradiation to HeLa cell line. They proved that topical corticosteroids regulated IL-6 expression.[17] These studies have established that topical steroids have the ability to suppress radiation-induced dermal toxicity. These studies have also established that levels of inflammatory cytokines causing ARD increased within the first 24 hours of radiation application.[16,17] This underlines the necessity of topical steroid application from the first day of radiotherapy irrespective of signs or stage of ARD.

Studies regarding topical corticosteroids in ARD have always yielded conflicting results. Researchers are constantly searching for innovative interventions to control ARD. It has been suggested that topical mometasone cream can be used to control ARD.[18,19] Mometasone is a synthetic corticosteroid. It is unique from other topical steroids in 3 ways –

i. Higher potency with lesser risk of skin atrophy.[13]
ii. Topical application lasts nearly 24 hours.[20]
iii. Strongly inhibits IL-6 during radiotherapy.[21]

Few studies have shown an effect of mometasone in reducing ARD in breast cancer and head and neck cancer [22,23]. Few studies have suggested that topical mometasone has higher anti-inflammatory activity and duration of action longer than betamethasone.[13,24–26.] But all studies have been done outside India. We could not find any study done in India.

## MATERIALS AND METHODS

### Aim



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To assess and compare efficacy and safety of 0.1 % mometasone furoate cream with 0.1 % betamethasone valerate cream in acute radiation dermatitis in patients undergoing radiotherapy for head and neck squamous cell carcinoma (HNSCC).

**Objectives**

- To assess the efficacy of 0.1 % mometasone furoate cream in acute radiation dermatitis in patients undergoing radiotherapy for HNSCC based on improvement in pain, itching and Radiation Therapy Oncology Group (RTOG) scores.
- To assess the efficacy of 0.1 % betamethasone valerate cream in acute radiation dermatitis in patients undergoing radiotherapy for HNSCC based on improvement in pain, itching and RTOG scores.
- To compare topical mometasone furoate with betamethasone valerate in terms of improvement in pain, itching, RTOG scores and development of adverse effects.

**Study Design**

This study was a prospective, comparative, open-label, randomized controlled trial conducted at Viswabharathi Cancer Hospital, Kurnool. For the purpose of randomization, the study population was categorized into 3 categories based on age group: 40 – 50 years; 51 – 60 years and 61 – 70 years. Each of these groups were subcategorized based on diagnosis and we had 3 subcategories: Nasopharyngeal carcinoma, Neck esophageal cancer and Hypopharyngeal carcinoma. Each of these subcategories were divided into 2 treatment groups: mometasone and betamethasone. As and when a participant was recruited for the study, he/she was first assigned to mometasone group based on the patient's age and diagnosis. When that subcategory was filled next patient in that subcategory was assigned to betamethasone group, thus taking care that equal number of patients are assigned in mometasone and betamethasone groups in each subcategory [Figure 1].

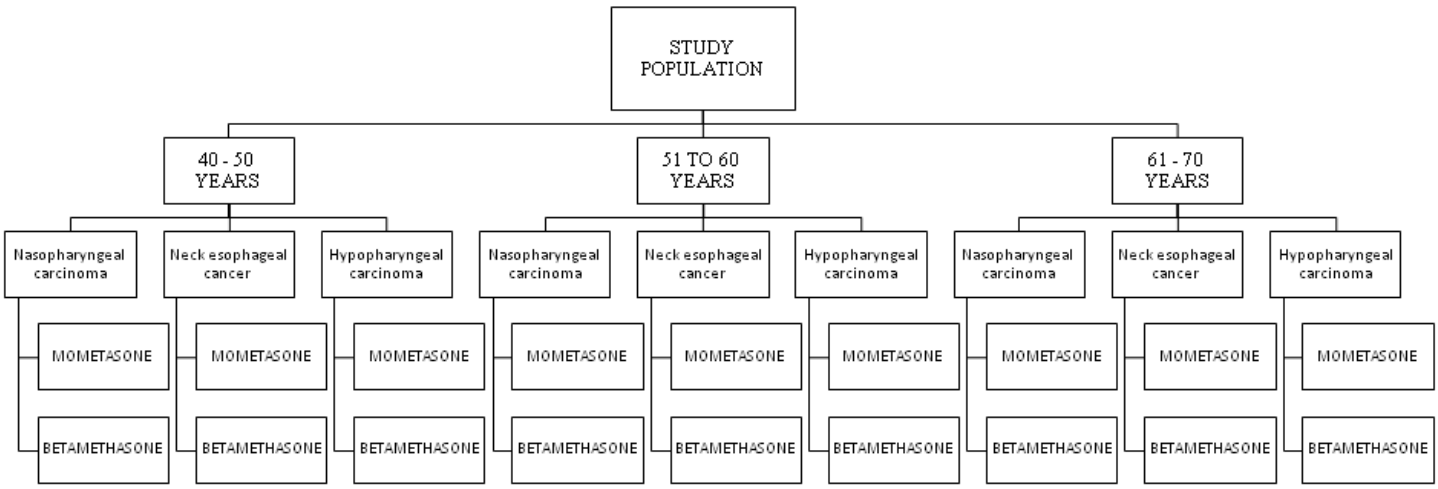


**Figure 1: Categorization Of Study Population For Randomization**

All participating patients were treated with radiotherapy. 5 – 8 MV photon energy by medical linear accelerator (LINAC) was used. Patients were instructed to wash their irradiated area with soap and water daily. Given cream was meant to be applied daily on the irradiated area and allowed to remain for around 18 hours continuously. Application of any other kind of topical agent during the treatment period was not allowed. Acute Radiation Dermatitis (ARD) was assessed twice, before initiating radiotherapy and 2 weeks after ending radiotherapy.

- ARD assessment included symptoms like pain, itching. Radiation Therapy Oncology Group (RTOG) scores for ARD were also assessed. RTOG scale was used in the following manner:[27]



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0=no visible change;

1=follicular, dark erythema with hair loss, dry peeling, and less sweating;

2=tender or bright erythema with or without moist desquamation, but with patchy moist desquamation with moderate edema;

3=confluent moist desquamation with pitting edema of the unfold skin;

4=necrotic, ulcer and bleeding.

- Pain and itch scores were divided into 3 stages in the following manner:

0=no pain or itch;

1=little pain or itch that did not affect daily sleep;

2=serious pain and itch that affected sleep.

ARD assessment was always done by 2 doctors individually. If both doctors had a difference in their assessments, then a third doctor was requested for an opinion and a consensus was reached. Radiotherapy plans of all patients were retrieved, skin target (along with 0.5cm of subcutaneous tissue) was outlined on accomplished radiotherapy plan, thus average dose for skin target was calculated[28] Mometasone/betamethasone application was stopped if there was aggravation of ARD or any other adverse event.

Prior permission was taken from the institutional ethics committee (EC/NEW/INST/2020/956) of Viswabharathi medical college and general hospital. Written informed consent was taken from all patients after explaining the process and reason for the study. The entire process of explanation and taking signature was video-recorded.

**Inclusion Criteria**

- Age: 18 – 75 years
- Histologically diagnosed primary HNSCC
- Posted for regular, fractionated, definite radiotherapy to the neck

**Exclusion Criteria**

- Pregnancy
- Lactation
- Allergic history to steroids and hormones.
- Skin infections/ulcers at the site of radiation
- Skin atrophy.

**Statistical Analysis**

The sample size was estimated keeping significance level as 0.05, power as 80 % and a dropout rate of 10 % for each group. We estimated our sample size to be 60 patients in each group. Our primary efficacy endpoint was a maximal reduction of RTOG score, the severity of pain and itching as stated above. Statistical comparisons of RTOG score, pain score and itch score were compared using Mann-Whitney U test. All p values were 2 sided. P-value < 0.05 was considered significant. SPSS was used to perform statistical analysis.

**RESULTS**

159 patients of HNSCC attending Viswabharathi Cancer hospital, Kurnool from February 2019 to January 2020 were recruited for this study. Patients were randomized into 2 groups such that they received only 1 of 2 treatments – mometasone furoate or betamethasone valerate. Care was taken to maintain similar demographics and baseline levels in both groups [Table 1]. 36 patients dropped out from the study as they had used other herbal medication along with test drug. So 123 patients were included in this study.

***Table 1. Patient Demographics***

| | | **Mometasone (n = 62; 50.41%)** | **Betamethasone (n = 61; 49.59%)** |
|---|---|---|---|
| | Age in years, Mean ± SD | 53.54±13.51 | 54.12 ± 12.69 |
| Tumor | Nasopharyngeal carcinoma | 44 (70.97%) | 43 (70.49%) |



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| | | | |
|---|---|---|---|
| | Neck esophageal cancer | 11 (17.74%) | 12 (19.67%) |
| | Hypopharyngeal carcinoma | 7 (11.29%) | 6 (9.84%) |
| | | | |
| Treatment | Cisplatin + Radiotherapy | 27 (43.55%) | 27 (44.26%) |
| | Paclitaxel + Radiotherapy | 30 (48.39%) | 28 (45.90%) |
| | Only Radiotherapy | 5 (8.06%) | 6 (9.84%) |
| | | | |
| Skin dose, cGy | < 6000 | 44 (70.97%) | 46 (75.41%) |
| | ≥ 6000 | 18 (29.03%) | 15 (24.59%) |
| | Skin dose, Mean ± SD, cGy | 5865.51 ± 245.17 | 5846.60 ± 225.38 |
| | | | |
| RTOG SCORES | 1 | 20 (32.26%) | 19 (31.14%) |
| | 2 | 34 (54.84%) | 34 (55.74%) |
| | 3 | 5 (8.06%) | 4 (6.56%) |
| | 4 | 3 (4.84%) | 4 (6.56%) |
| | | | |
| PAIN SCORE | 1 | 4 (6.45%) | 4 (6.56%) |
| | 2 | 58 (93.55%) | 57 (93.44%) |
| | | | |
| ITCH SCORE | 1 | 16 (25.80%) | 17 (27.87%) |
| | 2 | 46 (74.20%) | 44 (72.13%) |

Of these 123 patients, 54 patients received cisplatin chemotherapy with radiotherapy concurrently every 3 weeks, 58 patients received paclitaxel chemotherapy with radiotherapy every 3 weeks and 11 patients received only radiotherapy. Radiation was given in dose range of 5323 to 6378 cGy in 27 to 34 fractions for 5 to 8 weeks, 5 days per week. Calculation of Radiotherapy skin dose was done after radiotherapy.

We observed that in mometasone group, more no. of patients had their RTOG scores reduced from higher scores to 1 {39 (62.90 %) vs 18 (29.51 %)}. While in betamethasone group, more no of patients had their RTOG scores reduced from higher scores to 2 {15 (24.19 %) vs 39 (63.93 %)}. Not much change was observed in betamethasone group having an RTOG score of 1. The difference between mometasone and betamethasone for reducing RTOG scores was statistically significant ($p < 0.05$) [Table 2].

**Table 2: RTOG ARD Scores after Treatment**

| | **1** | **2** | **3** | **4** |
|---|---|---|---|---|
| **Mometasone (n=62)** | 39 (62.90 %) | 15 (24.19 %) | 6 (9.68 %) | 2 (3.23 %) |
| **Betamethasone (n=61)** | 18 (29.51 %) | 39 (63.93 %) | 3 (4.92 %) | 1 (1.64 %) |



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| | | | | |
|---|---|---|---|---|
| **p value** | < 0.05* | < 0.05* | | |
| ***indicates significant statistical difference** | | | | |
| RTOG=radiation therapy oncology group.<br>ARD=acute radiation dermatitis. | | | | |

Pain reduction to score 1 was more in mometasone group vs betamethasone group {58 (93.55 %) vs 42 (68.85 %)}. Similarly, itch reduction to score 1 was more in mometasone group compared to betamethasone group {59 (95.16 %) vs 47 (77.05 %)} [Table 3].

**Table 3: Pain and ITCH Scores after Treatment**

| | PAIN SCORE | | ITCH SCORE | |
|---|---|---|---|---|
| | **1** | **2** | **1** | **2** |
| **Mometasone (n=62)** | 58 (93.55 %) | 4 (6.45 %) | 59 (95.16 %) | 3 (4.84 %) |
| **Betamethasone (n=61)** | 42 (68.85 %) | 19 (31.15 %) | 47 (77.05 %) | 14 (22.95 %) |
| **p value** | < 0.001* | | < 0.001* | |
| ***indicates significant statistical difference** | | | | |

We had also analyzed changes in RTOG scores according to radiotherapy dose since RTOG score is directly related to the dose of radiotherapy. We observed that both mometasone and betamethasone valerate were effective when radiotherapy dose was < 6000 cGy and this difference compared to baseline was statistically significant ($p < 0.001$). On the other hand, both the steroids had less efficacy when radiotherapy dose was > 6000 cGy ($p > 0.05$) [Table 4].

**Table 4: RTOG Scores of Skin Radiotherapy Dose <6000 cGy and ≥6000 cGy after treatment**

| | < 6000 cGy | | | > 6000 cGy | | | | |
|---|---|---|---|---|---|---|---|---|
| **ARD RTOG score** | **1** | **2** | **p-value** | **1** | **2** | **3** | **4** | **p-value** |
| **Mometasone (n=62)** | 35 (56.45 %) | 11 (17.74 %) | < 0.001 | 3 (4.84 %) | 5 (8.06 %) | 6 (9.68 %) | 2 (3.23 %) | > 0.05 |
| **Betamethasone (n=61)** | 10 (16.39 %) | 34 (55.73 %) | | 3 (4.92 %) | 4 (6.56 %) | 6 (9.84 %) | 4 (6.56 %) | |
| | | | | | | | | |
| RTOG=radiation therapy oncology group.<br>ARD=acute radiation dermatitis | | | | | | | | |

No adverse effects like atrophic dermatitis, telangiectasia, or eczema were seen in any participant.

## DISCUSSION

Acute radiation dermatitis (ARD) occurs commonly in patients with breast cancer, lung cancer and head



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and neck cancers since higher radiation doses are needed in these cases [9]. ARD has such a detrimental effect on the skin and quality of life of a patient, that it can also lead to treatment interruption [7]. Interruptions in treatment further results in lengthening of radiotherapy which often results in loss of control over cancer growth [29]. Topical steroids have been known to delay the onset and progress of ARD and have thus contributed to improving quality of life. Steroids have proved their efficacy against placebo and emollients.[30]

Multinational Association for supportive care in cancer skin toxicity had suggested that corticosteroids have a good role in reducing ARD.[31] Kole et. al., 2014 published evidence about the role of corticosteroids in their systematic review.[26] Similarly Omidvari et al demonstrated the efficacy of betamethasone in preventing ARD in breast cancer patients undergoing radiotherapy.[19] Bostrom et al established the efficacy of mometasone furoate cream in ARD for patients of breast cancer undergoing radiotherapy.[22] Few clinical trials have compared mometasone vs betamethasone in breast cancer and they were of opinion that mometasone is more efficacious than betamethasone.[18,32,33]

Further, most of these studies have focused on breast cancer. Very few studies have focused on head and neck cancer.[23,34] When we searched for similar studies done in Indian population, we came across two studies by Sunku et al and Menon et al where they compared topical betamethasone with placebo for ARD in patients of HNSCC.[30,35] But we could not find any study where mometasone has been compared with betamethasone for ARD in HNSCC in Indian population. So our study is the first of its kind.

We observed in this study that patients benefitted more from mometasone compared to betamethasone as mometasone can bring down RTOG score to 1 but betamethasone can bring down RTOG score to 2. Our results have proved that mometasone application after radiotherapy is good in preventing ARD compared to betamethasone topical application. Both these drugs have good efficacy when radiotherapy dose is < 6000 cGy. Our study was effective in not only reducing RTOG score but also pain and itch. This can be contributed to the decrease of IL-6 by mometasone and betamethasone.[36] Amelioration of itching can also be attributed to the reduction of histamine by mometasone and betamethasone.[36] Moriyasu et al. established the role of histamine in the development of radiation-induced dermatitis. They demonstrated that inflammation never occurred when mice deficient in mast cells were given radiation. They also demonstrated how blocking H1 receptors by antihistamines prevented dermal inflammation.[37]

Our results are similar to previous studies where the efficacy of betamethasone, mometasone or other corticosteroids were used against ARD.[29,30] Our study has also proved good efficacy in lowering pain, itch and RTOG score. Our study results also corroborate with previous studies in side effect profiles. Both drugs were safe and no major adverse effects were seen (29,30).

India is a developing country. Cancer diagnosis in most Indian patients is done at higher age where the cancer stage is often in an advanced stage.[38] Indian population differs from population of rest of the world in various terms related to incidence and prevalence of ARD.[5] Skin of Indians is different from westerners when it comes to duration and intensity of sunlight exposure, melanin concentration, the composition of sebum, and hydration level.[39] Around one-third of patients undergoing treatment for cancer in India are in the geriatric age group.[40] Geriatric age group have a lesser physiological reserve in their skin. The skin of older individuals often has more aged cells, thickened epidermis, lack of collagen, and a sparser capillary network. Hence older patients are more susceptible to any toxicity due to radiation. Recovery after any kind of injury including radiation is quite delayed in older individuals owing to specific nutritional deficiencies, other comorbidities, preexisting dermatological diseases and allergies.[41] Since India is a developing country, cancer patients have restricted access to healthcare. As radiotherapy is a month-long process, patients have to travel long distances with minimal resources to hospitals. Hygienic food and accommodation are a luxury for many such families during radiotherapy sessions. Poor nutrition and sanitation contribute to delay in skin healing post-radiotherapy. [8,42]

ARD severity is dependent on treatment-related and patient-related factors. Researchers have been able to control treatment factors but not patient factors – skincare habits, medicines, diabetes, kidney failure,



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elderly, continuous sun exposure, smoking and other environmental conditions.[43] Major symptoms of ARD – pain and itch are subjective. Every patient has different sensitivity towards pain and itch, and these are influenced by subjective emotions, previous experiences, lifestyle, etc.[44] Liao et al studied the efficacy of corticosteroids on ARD in HNSCC where they divided the neck into two anatomical sections right and left. One section was given a corticosteroid while the other was not given any treatment. Such division was done for self-comparison of subjective symptoms like pain and itch [34]. However, we could not carry out such a method due to ethical limitations from IEC and consent limitations from patients. Future studies may be carried out in such a manner for a better comparison of subjective factors. Ryan et al had demonstrated that ARD is more severe in blacks.[45] We could not include the racial aspect in our study.

Regarding treatment-related factors, concurrent chemoradiotherapy increases the severity of ARD.[46] In addition different anti-cancer drugs have a varied response to skin toxicity. For example, 5 fluorouracil is well known for its adverse effects on the skin.[47,48] Effect of different anti-cancer drugs was not considered in our study. It has also been published that ARD manifestation varies with season. Patchy, dry peeling of skin occurs in winter and wet desquamation occurs in summer.[34] This point should also be taken into consideration in further studies.

## CONCLUSION

Mometasone furoate local application after radiotherapy is efficacious in controlling Acute Radiation Dermatitis especially when the skin dose is < 6000 cGy and this effect of mometasone is better than betamethasone valerate local application. The risk of side effects too is minimal with topical mometasone.

## DECLARATIONS

### Ethics approval and consent to participate

Prior permission was taken from the institutional ethics committee (EC/NEW/INST/2020/956) of Viswabharathi medical college and general hospital. Written informed consent was taken from all patients after explaining the process and reason for the study.

**Consent for publication** – Not Applicable

**Availability of data and materials** – Not Applicable

**Conflicts Of Interest:** Authors declare no conflict of interest.

**Funding** – Not Applicable

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