

## **Pamidronate Disodium Versus Calcitonin: A Comparative Study in the Management of Malignant Bone Pain in Metastatic Breast Cancer Patients**

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### **ABSTRACT**

This prospective study was conducted on 60 female patients, complaining of painful bone metastases from breast cancer. The patients were randomly allocated to one of three groups according to the drug received, pamidronate group received 60 mg/2 weeks for three months, calcitonin group received 100 IU S.C. / day daily for 14 days and then day after day for the rest of the study, and combination group received combination of the two regimens. Patients were evaluated for vital signs, Visual Analogue Scale V.A.S., and biochemical parameters: serum calcium, serum bone alkaline phosphatase, urinary calcium, urinary creatinine and urinary hydroxyproline. Significant decrease in bone pain scoring was found in pamidronate and combination groups. Calcitonin was found to be more hypocalcaemic with rapid action. Combining the two drugs makes benefit from the rapid onset of calcitonin and the delayed but long acting action of pamidronate in dealing with hypercalcaemia of malignancy. Minimal side effects, as nausea and vomiting, post infusion pyrexia, bone pain etc., had been found in the three groups.

**Key Words:** *Pamidronate - Calcitonin - Breast cancer - Bone metastases - Malignant hypercalcaemia.*

### **INTRODUCTION**

Metastatic cancer invades bone in 60-84% of cases, which is more often seen with lung and prostatic cancer in males and cancer of the breast in females. As regards breast cancer, the most common affected sites are the thoracic and lumbar vertebrae, femur, and the skull. Pain develops gradually during a period of weeks or months, becoming progressively more severe. It is usually localized in a particular area and often felt at night or on weight bearing. Pain is characteristically described as dull in character, constant in presentation, gradually progressive

in intensity, and increases with pressure on the the area affected [15].

Metastatic bone pain may be attributable to stretching of the periosteum by tumor expansion, mechanical stress of the weakened bone, nerve entrapment by the tumor or direct destruction of bone with consequent collapse [9].

Bisphosphonates probably play a role in the cascade of cellular, biochemical, and physiological events that lead to osteoclastic bone resorption, either by influencing the recruitment of mononuclear cells or by inhibiting the activity of osteoclasts [8]. Pamidronate is the most potent available biphosphonates [12]. Using 60 mg of pamidronate given intravenously every two weeks, a significant reduction in pain was found after one month in breast cancer patients with bone metastases [20].

Calcitonin, being a hypocalcemic drug, may be useful as adjuvant analgesic for metastatic bone pain. It inhibits sodium and calcium absorption by renal tubules and reduces osteoclastic bone resorption. However, the role of calcitonin appears to be limited by its short duration of action and poor efficacy for the rapid development of tachyphylaxis, despite its rapid effect [16].

This work was planned to study the efficacy of pamidronate disodium, given alone or combined with clacitonin, versus calcitonin as a new strategy in the relief of bone pain in patients with metastatic breast cancer.

## PATIENTS AND METHODS

This work was conducted on 60 female breast cancer patients, chosen from the Pain Clinic of the National Cancer Institute, Cairo University between 1998 and 2000, after admission and establishment of diagnosis.

### *Criteria of patients:*

Our patients were females between 42-64 years, complaining from breast cancer with severe pain from multiple bone metastases not responding to ordinary analgesics.

Exclusion criteria were: patients previously exposed to pamidronate therapy or calcitonin within 90 days or radiation therapy within two weeks before the study; history of pathologic fractures or epidural spinal cord compression within the previous 3 months; patients with single bone metastatic lesion, who made benefit from peripheral nerve blocks; and patients showing serum creatinine >2.0 mg/dl, leukocytic count <3.5 x 10<sup>9</sup>/L, hematocrit <30%, platelet count <100 x 10<sup>9</sup>/L, ascites, total bilirubin >2.5 mg/dl, or clinically significant ECG changes.

### *Grouping:*

Patients were randomly allocated to one of the following groups according to the drug received:

- 1- **Group 1** "*Pamidronate group*": (20 patients), all of them received pamidronate disodium "Aredia" in a dose of 60 mg as an infusion of 125 ml/hour for 4 hours every two weeks for a period of three months.
- 2- **Group 2** "*Calcitonin group*": (20 patients), all received calcitonin 100 IU S.C./day, daily for two weeks then day after day till the end of the study which is three months.
- 3- **Group 3** "*Combination group*" (20 patients), this group received pamidronate disodium 60 mg as an infusion of 125 ml/hour for 4 hours every two weeks for a period of three months in combination with calcitonin 100 IU S.C./day, daily for two weeks then day after day till the end of the study.

### *Evaluation:*

Patients were evaluated at the start of the study and every two weeks for three months for all variables except serum calcium level which was evaluated daily for the first two weeks then

every two weeks till the end of the study, and radiological bone lesion response which was evaluated only at the start and at the endpoint of the study.

**Vital signs:** were measured at the start and completion of every pamidronate infusion, and the site of infusion was monitored closely for signs of inflammation.

**Visual Analogue Scale "VAS":** The patients' pain level was evaluated by having the patient mark at a 100 mm VAS, this gave us the pain severity level of each patient.

### **Laboratory Investigations:**

At baseline and every two weeks, these included:

- Biochemical parameters: Serum bone alkaline phosphatases: Using a colorimetric determination kit (by BioMerieux SA, France) [1], Urinary hydroxyproline: to quantitate the excretion of deoxypyridinoline crosslinks as an indicator of bone resorption, results are corrected for urinary concentration of creatinine [6], Serum calcium and urinary calcium: are determined by atomic absorption spectroscopy with the aid of automated analyzers.
- Routine: complete blood picture, liver function test "AST- ALT-serum bilirubin" and renal function tests "S.urea and creatinine" and urinary creatinine are also determined.

### **Radiological bone lesion response:**

This was evaluated by bone scanning and X-ray at the site of metastases as baseline and endpoint, and then compared by a radiologist (who was not informed of the treatment group).

### **Statistical Analysis:**

Descriptive statistics as presented in frequency tables, means ± standard deviation whenever appropriate. ANOVA with repeated measures was used for comparing means of more than two groups. Chi Square test was used for contingency table analysis. Significance levels of 0.05 and 0.01 were used throughout all statistical tests within the study.

## RESULTS

Three patients were excluded from the study, two in the pamidronate group (one died after one month and the other required chemotherapy for liver metastases), while one died in

the combined group after 5 weeks. The most common analgesic given as required by patients during the study was Morphine as (MST sustained release tablets) 60-20 mg/day, which was stopped by patients one day before every evaluation point.

Table (1): Patients' characteristics at the start of the study in the three treated groups.

Criteria	Group		
	I Pamidronate	II Calcitonin	III Combination
No.	20	20	20
Age (range)	(43-64)	(45-62)	(42-60)
<b>Prior treatment:</b>			
Radical Mastectomy	12	14	10
Radiotherapy	16	17	12
Chemotherapy	6	10	14
<b>Bones affected:</b>			
Lumbar vert.	13	14	12
Femur	8	9	8
Skull	2	-	3

**Visual Analogue Score "V.A.S.":**

Our study showed that the Visual Analogue Score was significantly decreased in the pamidronate treated and combination treated group ( $p < 0.01$ ). Meanwhile, in the calcitonin treated group there was a significant decrease on 2<sup>nd</sup> week with no further decrease all through the study evaluation points. At the endpoint evaluation, pamidronate and combination treated groups showed a significant decrease over calcitonin group ( $p < 0.05$ ) Table (2).

Table (2): Visual Analogue Score (millimeter) at different weeks, in the different treated groups as "Mean ± Standard deviation".

Weeks	Group		
	Pamidronate (n=18)	Calcitonin (n=20)	Combination (n=19)
Baseline	82.7 (±8.2)	81.5 (±8.3)	83.2 (±8.5)
Week 2	78.1 (±6.8)	55.8* (±9.8)	53.2* (±12.2)
Week 4	65.0 (±12.8)	58.3 (±8.3)	49.5* (±9.7)
Week 6	49.4* (±6.8)	59.3 (±9.1)	49.2* (±10.7)
Week 8	35.1** (±6.6)	60.5 (±8.6)	42.9** (±11.1)
Week 10	33.9** (±6.3)	60.5 (±9.2)	42.4** (±8.7)
Week 12	32.8** (±7.3)	58.8 (±10.0)	40.3** (±9.8)
Week 14	30.3** (±6.1)	59.0 (±9.7)	38.2** (±9.2)

\* Significant difference from baseline value,  $0.01 < P < 0.05$ .  
 \*\* Significant difference from baseline value,  $P < 0.01$ .

**Changes in Serum Calcium Level**

We evaluated serum calcium daily during the first two weeks of study after the first injection and then every two weeks.

**1- Daily Serum Calcium Level in the first two weeks:**

In the pamidronate treated group, serum calcium level started to fall within the first seven days (days 5,6) reaching around normal levels on 14<sup>th</sup> day. No clinical episodes of hypo / hypercalcaemia were observed during study. In calcitonin treated and combination treated groups, serum calcium level started to fall within the first 24 hours reaching normal values after 10 days. These changes are shown in fig. (1).

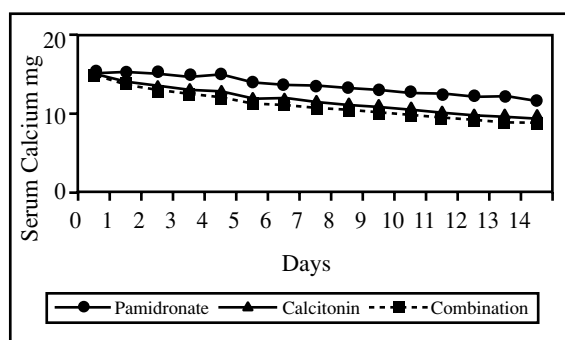


Fig. (1): Daily serum level in the first two weeks.

**2- Serum Calcium Level after the first two weeks:**

From our data, as shown in fig. (2), there was a highly significant decrease in the serum calcium level in the three groups at the end point. In pamidronate treated and combination treated group the decrease then was gradual till the endpoint. In calcitonin treated group, the marked decrease in mean serum calcium was on 2<sup>nd</sup> week then was raised again to a little higher level till the endpoint where it was still lower than baseline values with a highly significant  $p$ - value ( $< 0.01$ ). In combination treated group: three cases showed marked hypocalcaemic crises, which required calcium administration.

**Changes in Serum Bone Alkaline Phosphatase:**

From data obtained, as shown in table (3), there was a highly significant decrease in serum level of bone alkaline phosphatase in pamidronate treated and combination treated groups. Meanwhile, a less significant decrease was not-

ed in calcitonin treated group on 2<sup>nd</sup> week with no statistical significance between this value and the values obtained at the other evaluation points.

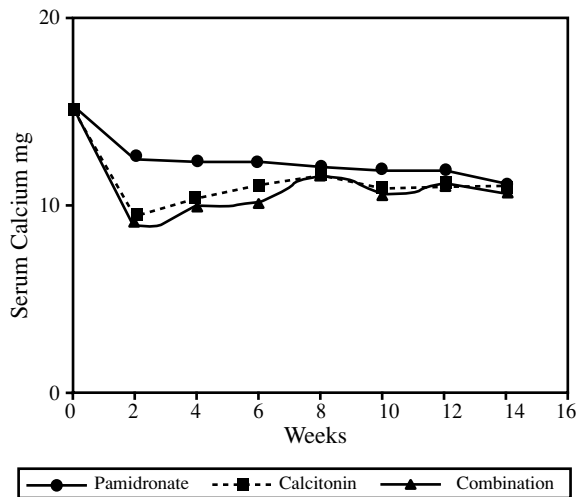


Fig. (2): Serum calcium level after the first two weeks.

Table (3): Bone Alkaline Phosphatase ( U/L ) on different weeks, in the different treated groups as "Mean  $\pm$  Standard deviation".

Weeks	Group		
	Pamidronate (n=18)	Calcitonin (n=20)	Combination (n=19)
Baseline	156.1 ( $\pm$ 12.02)	149.1 ( $\pm$ 11.16)	150.2 ( $\pm$ 11.83)
Week 2	80.0** ( $\pm$ 7.19)	127.1 ( $\pm$ 10.17)	83.1** ( $\pm$ 6.19)
Week 4	79.5** ( $\pm$ 6.93)	125.2 ( $\pm$ 9.94)	81.2** ( $\pm$ 7.07)
Week 6	75.3** ( $\pm$ 6.35)	121.2 ( $\pm$ 9.52)	79.1** ( $\pm$ 7.31)
Week 8	76.2** ( $\pm$ 6.53)	120.3 ( $\pm$ 9.63)	85.2** ( $\pm$ 7.11)
Week 10	74.4** ( $\pm$ 6.21)	118.5 ( $\pm$ 8.24)	82.6** ( $\pm$ 7.05)
Week 12	73.2** ( $\pm$ 6.21)	115.2 ( $\pm$ 8.17)	80.1** ( $\pm$ 6.94)
Week 14	72.1** ( $\pm$ 5.94)	117.1 ( $\pm$ 8.01)	76.3** ( $\pm$ 6.06)

\* Significant difference from baseline value,  $0.01 < P > 0.05$ .

\*\* Significant difference from baseline value,  $P < 0.01$ .

#### Changes in Urinary Calcium/Creatinine Ratio:

Table (4) shows a significant decrease in the urinary calcium / creatinine ratio in the pamidronate treated group starting from the 2<sup>nd</sup> week till the endpoint at 14<sup>th</sup> week. Meanwhile, in calcitonin treated and combination treated groups the significant decrease on 12<sup>th</sup> and 14<sup>th</sup> weeks was preceded by a transient increase above baseline values at weeks 2,4,6,8 for calcitonin treated group and weeks 2,4 for combination treated group.

Table (4): Urinary Calcium / Creatinine ratio at different weeks, in the different treated groups as "Mean  $\pm$  Standard deviation".

Weeks	Group		
	Pamidronate (n=18)	Calcitonin (n=20)	Combination (n=19)
Baseline	0.28 ( $\pm$ 0.16)	0.23 ( $\pm$ 0.15)	0.25 ( $\pm$ 0.11)
Week 2	0.21* ( $\pm$ 0.12)	0.31 ( $\pm$ 0.09)	0.27 ( $\pm$ 0.09)
Week 4	0.19* ( $\pm$ 0.14)	0.29 ( $\pm$ 0.08)	0.26 ( $\pm$ 0.08)
Week 6	0.19* ( $\pm$ 0.13)	0.27 ( $\pm$ 0.11)	0.20 ( $\pm$ 0.07)
Week 8	0.18* ( $\pm$ 0.13)	0.24 ( $\pm$ 0.07)	0.19 ( $\pm$ 0.08)
Week 10	0.16* ( $\pm$ 0.09)	0.20* ( $\pm$ 0.09)	0.19 ( $\pm$ 0.08)
Week 12	0.14** ( $\pm$ 0.08)	0.19* ( $\pm$ 0.08)	0.16* ( $\pm$ 0.09)
Week 14	0.14** ( $\pm$ 0.09)	0.19* ( $\pm$ 0.07)	0.14** ( $\pm$ 0.08)

\* Significant difference from baseline value,  $0.01 < P > 0.05$ .

\*\* Significant difference from baseline value,  $P < 0.01$ .

#### Changes in Urinary Hydroxyproline / Creatinine ratio:

Our data showed a significant decrease in the urinary hydroxyproline / creatinine ratio on 14<sup>th</sup> week (endpoint) in the pamidronate treated and combined treated groups as shown in table (5). As regards the calcitonin treated group there was a non-significant decrease all through the study.

Table (5): Urinary Hydroxyproline / Creatinine ratio on different weeks, in the different treated groups as "Mean  $\pm$  Standard deviation".

Weeks	Group		
	Pamidronate (n=18)	Calcitonin (n=20)	Combination (n=19)
Baseline	0.15 ( $\pm$ 0.09)	0.17 ( $\pm$ 0.08)	0.16 ( $\pm$ 0.09)
Week 2	0.12 ( $\pm$ 0.07)	0.16 ( $\pm$ 0.07)	0.11 ( $\pm$ 0.07)
Week 4	0.11 ( $\pm$ 0.05)	0.16 ( $\pm$ 0.06)	0.11 ( $\pm$ 0.06)
Week 6	0.11 ( $\pm$ 0.04)	0.15 ( $\pm$ 0.09)	0.12 ( $\pm$ 0.07)
Week 8	0.12 ( $\pm$ 0.04)	0.14 ( $\pm$ 0.07)	0.12 ( $\pm$ 0.08)
Week 10	0.12 ( $\pm$ 0.07)	0.14 ( $\pm$ 0.07)	0.11 ( $\pm$ 0.08)
Week 12	0.10* ( $\pm$ 0.06)	0.13 ( $\pm$ 0.06)	0.10* ( $\pm$ 0.06)
Week 14	0.08* ( $\pm$ 0.02)	0.14 ( $\pm$ 0.08)	0.08* ( $\pm$ 0.04)

\* Significant difference from baseline value,  $0.01 < P > 0.05$ .

\*\* Significant difference from baseline value,  $P < 0.01$ .

#### Radiological Findings at endpoint:

As shown in table (6), pamidronate treated group showed partial response in 5 patients (27.8%) while in the other 13 patients (72.2%) the radiological findings were stable. In the calcitonin treated group, 4 patients (20%) had partial response and 16 patients (80%) had stable findings. On the other hand, in combination

treated group, 7 patients (36.8%) showed partial response and 12 patients (63.2%) had stable findings. There was insignificant change between the three groups in this study.

Table (6): Radiological findings at the end of study among the different treated groups

Response	Group					
	Pamidronate (n=18)		Calcitonin (n=20)		Combination (n=19)	
	No.	%	No.	%	No.	%
Partial response	7	38.9%	4	20%	7	36.8%
Stable disease	11	61.1%	16	80%	12	63.2%

Chi - square = 1.930

$p=0.381$ (not significant)

## DISCUSSION

In the current study, pamidronate disodium in a dose of 60 mg/2 weeks is compared to calcitonin 100 IU (SC) / day in the management of bone metastases in patients with breast cancer. Meanwhile, a third group is added, “the combination group” to study the effect of combination of the rapid hypocalcemic effect of calcitonin with the delayed effects of pamidronate. Regarding pain relief changes in this study, there was a significant decrease in bone pain score and Visual Analogue Scale (VAS) scoring in the pamidronate and combination groups which started at weeks 4 and 2, respectively, and reached a high significant level at the end of the study ( $p<0.01$ ). The calcitonin group showed a decrease in these scores but it was statistically insignificant. This is in agreement with the studies done by Tyrrel et al. [20,21], when 60 mg of pamidronate were given intravenously every two weeks with a resultant significant reduction in pain after one month in breast cancer patients with bone metastases. The effect of pamidronate on malignant bone pain was also shown in the study of Conte et al. [4] where there was a marked relief of bone pain. This finding was supported by the results of Lipton et al. [14] and Koeberle et al. [13] on pamidronate 60 mg/2 weeks where the pain reduction by the end of their studies was statistically significant. Meanwhile, in the calcitonin group there was a significant decrease in pain score at the end of the 2<sup>nd</sup> week with no further decrease. At endpoint evaluation, a comparison between the 3 groups revealed a highly significant decrease in the pa-

midronate and combination groups over the calcitonin group ( $p<0.05$ ).

Antibodies to calcitonin, particularly to salmon calcitonin, develop in a significant population of patients receiving long-term treatment [17]. There is some concern that these antibodies may diminish the efficacy of calcitonin [19], this was called “Escape phenomenon”. These antibodies are responsible for the diminishing effect of calcitonin in consequent evaluations. When combination of pamidronate and calcitonin was used, we made use of the significant rapid onset effect of calcitonin beside the slightly delayed but long acting effect of pamidronate with no toxicity. This was in agreement with the study by Koeberle et al. [13], when pamidronate, 60 mg, was given to patients with malignant bone pain, a trend toward improved pain severity and decrease in analgesics consumption was also observed. These findings may come in contrast with those found by Hultborn et al. [11] when they found a statistically insignificant lower consumption of opioid analgesics in pamidronate (60 mg/4 weeks) group ( $p=0.14$ ), but this was explained by the less frequency of dosing which might have given these results, as explained by Lipton et al. [14] who found a dose-related reduction in pain score.

In the current study, determining the serum calcium level was a cornerstone in evaluating the effect of these drugs on osteoporotic events in bones. With the baseline values of the three studied groups quite similar, there was a highly significant ( $p<0.01$ ) decrease in serum calcium level at endpoint. During the first 14 days, serum calcium started to be lowered on the 5<sup>th</sup> day in pamidronate group (14.1±7.2 mg/dl) and reached a quite normal value on 14<sup>th</sup> day (11.8±6.3 mg/dl). In calcitonin and combination groups it started to fall from the 2<sup>nd</sup> day reaching normal value on the 7<sup>th</sup> day (11.0±6.4 mg/dl) continuing to lower till (9.2±6.1 mg/dl) in the combination group on 14<sup>th</sup> day. These results were nearly the same as mentioned by Sekine and Takami [18] who combined the rapid hypocalcaemic effects of calcitonin with the delayed effects of pamidronate where the serum calcium level decreased to normal within 4 days with the mean calcium level falling from 15.3 mg/dl to 9.2 mg/dl. Calcitonin exerts a calcium-lowering effect both through its direct inhibiting effect on osteoclastic bone resorption and prevention of calcium reabsorption from re-

nal tubules. It has the most rapid onset of action, which appears within few hours after administration, but continued usage diminishes its effect [7].

Regarding pamidronate, the P-C-P bond in its structure leads to avid binding to hydroxyapatite crystals making it difficult for osteoclasts to recognize exposed unmineralized bone surfaces [5]. Bisphosphonates are directly toxic to osteoclasts, causing small fall in serum calcium on the first days, but this effect becomes greater after 3-7 days [3]. In the current study, despite the significantly decreased serum calcium level in the three groups, changes from the values of the 2<sup>nd</sup> week evaluation were insignificant through all the consequent values. On the other hand, 3 patients (15.8%) in the combined group showed marked hypocalcaemia with mild tetany and parasthesia of the finger tips of both hands, which is thought to be due to rapid inhibition of osteoclast-mediated bone resorption. Whilst osteoblast-mediated bone formation continues, this causes a net influx of calcium into bone as noted by Body and Dumon [2]. Concerning serum bone alkaline phosphatase, which reflects osteoblast activity, the current study showed a highly significant decrease in serum level in pamidronate and combination group, meanwhile less significant decrease was found in calcitonin group on 2<sup>nd</sup> week with no significance between this value and values obtained at other evaluation points. Fall in the serum bone alkaline phosphatase in 66% of calcitonin treated patients was also observed by Siminoski and Robert [19], but it relapsed again, which may be explained by the formation of neutralizing antibodies. In the current study, urinary calcium and hydroxyproline were corrected for urinary concentration of creatinine to increase the power of results as previously described by Eastell et al. [6].

Urinary calcium / creatinine ratio showed a significant decrease ( $p < 0.05$ ) in the pamidronate group starting from 2<sup>nd</sup> week till endpoint on 14<sup>th</sup> week. Meanwhile, in calcitonin and combined groups the significant decrease on 12<sup>th</sup> and 14<sup>th</sup> week was preceded by a transient increase above baseline values on weeks 2, 4, 6 and 8 for calcitonin group and weeks 2 and 4 for combined group. Glover et al. [10] showed the same results with pamidronate 60 mg/2 weeks. The initial increase in this ratio showed from the data obtained in calcitonin and combi-

nation groups was explained by Eto et al. [7] as prevention of calcium reabsorption from renal tubules by calcitonin. This advantage was also explained as the "Calciuric Effect" of calcitonin.

Data from the current study showed significant decrease in urinary hydroxyproline / creatinine ratio in the pamidronate and combination groups at endpoint. This was in agreement with the results obtained by Glover et al. [10] and Sekine and Takami [18]. In the calcitonin group, the current study showed an insignificant decrease in urinary hydroxyproline / creatinine ratio all through the study ( $p > 0.05$ ). At endpoint evaluation, 7 patients (38.9%) had X-ray findings consistent with a partial response in bone with pamidronate therapy, with no change (stable) in 11 patients (61.1%). In the calcitonin group, 4 patients (20%) had partial response and 16 patients (80%) had stable findings. Pamidronate group showed partial response in 7 patients (36.8%) and stable disease in 12 patients (63.2%) with no significant change between the three groups.

In the current study, some side effects have been noticed, post infusion pyrexia in 6 patients (33.3%) in pamidronate group and 8 patients (42.1%) in combination group. Temperature ranged from 38-39°C, started after 24 hours and subsided within 48-72 hours, mainly encountered after the first infusion. Mild phlebitis was noticed in 4 patients (22.2%) in pamidronate group at the site of infusion and in 2 patients (10.5%) in combination group. Bone pain and myalgia were encountered in 2 patients (11.1%) in pamidronate group and in 4 patients (21.1%) and 2 patients (10.5%), respectively, in calcitonin and combination groups. Nausea and vomiting were the most frequent side effects of calcitonin group with an incidence of nausea of 30% (6 patients) which was evident after the first injection. Regarding the combination group, its incidence was 42.1% (8 patients), lasting for 4-6 hours, reduced to 1-2 hours with the administration of 10 mg metoclopramide I.V. The exact mechanism for this is still unknown but it is probably due to the central effect of calcitonin.

#### Conclusion:

Pamidronate disodium (one of the bisphosphonates) has been proven to be more effective than calcitonin in the management of bone pain

resulting from metastatic cancer breast, meanwhile calcitonin was superior in its rapid hypocalcaemic effect compared with the delayed but long acting effect of pamidronate. Decrease in biochemical markers are consistent with inhibition of osteoclastic activity and is also shown with pamidronate more than calcitonin. The combination of the two drugs was shown to be well tolerated and more effective with the gain of the rapid effect of calcitonin and the delayed but long acting action of pamidronate with no resultant severe side effects.

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