Prevalence, initiating factor and treatment outcome of medication-related osteonecrosis of the jaw - a four year prospective study. *29.June 2018*

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ABSTRACT

Objectives: Prevalence of MRONJ is reported with a wide range and a standard therapy has not yet been established. The aim of the study was to analyse the prevalence, initiating factors and the outcome of surgical therapy.

Study design: In a prospective cohort study, all patients diagnosed 2012 to 2015 with MRONJ in the region of Skåne were included. Predictor variables (co-morbidity, site, stage, gender) and initiating factors (tooth extraction, periodontitis) were recorded. Surgical treatment was subdivided into sequestrectomy or block resection and the treatment outcome variable was healing after 2 months. To estimate the prevalence, data on the use of bisphosphonate and denosumab were obtained from *www.socialstyrelsen.se*.

Results: Fifty-five patients with MRONJ were identified, 43 women (mean age 73.1 years) and 12 men (mean age 63.6 years). The prevalence of MRONJ for patients on oral bisphosphonates was estimated to be 0.043%, intravenous bisphosphonates 1.03% and in patients on high dose denosumab 3.64%. Periodontal disease preceded development of MRONJ in a total of 41 patients. Five patients were excluded and 50 were treated surgically and followed up for periods of 2-46 months (mean 15.7 months). In 10 patients treated with sequestrectomy, 8 lesions (80.0%) progressed to remission or healing. In 40 patients treated with block resection, 37 lesions (92.5%) progressed to remission or complete healing.

Conclusion: The prevalence of MRONJ in Sweden is low. Periodontitis is the most common initiating factor. The treatment outcome of MRONJ demonstrates healing in most patients treated surgically.

Key words: Osteonecrosis of the jaw; Bisphosphonate; Denosumab; Prevalence; Treatment

INTRODUCTION

The antiresorptive drugs bisphosphonates (BPs) and denosumab are widely, efficiently, and safely used in osteoporosis to preserve and strengthen existing bone by increasing its mineralization, to treat hypercalcemia of malignancy and bone metastasis of solid malignant tumors [1–5]. Intravenous BPs and denosumab are mainly used in patients with metastatic bone disease such as metastatic breast cancer and metastatic prostate cancer or in multiple myeloma [2–5]. In patients with osteoporosis, oral BPs are mostly used. In some patients that do not tolerate oral BPs, zoledronic acid can be used as an annual infusion or denosumab as subcutanous injection twice a year for the treatment of osteoporosis [2,6]. Bisphosphonates inhibit bone resorption, bone turnover and renewal through inhibition of the osteoclast activity [7,8].

Denosumab is an IgG2 monoclonal antibody with affinity and specificity for RANK ligand (RANKL) that inhibits RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of RANKL-RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption [2].

Medication-related osteonecrosis of the jaw (MRONJ) is reported as a serious side effect associated both with BPs and denosumab treatment. The first report on MRONJ came in 2003 and after this, numerous cases of non-healing exposed, necrotic bone in the maxillofacial region have been reported in patients treated with BPs or denosumab [9–11].

Data from a retrospective study carried out in the same region as the present study reported a prevalence of MRONJ in patients on oral BPs to be 0.024% and 2.8% in patients on intravenous treatment [11]. Prevalence of MRONJ is reported in studies from different parts of the world with a wide range of 0-27.5% [12,13].

The pathogenesis of MRONJ is still debated but recent data suggest that odontogenic infections such as periodontitis might play a crucial role and contribute to the development of disease. A recent study showed that the necrotic bone lesions contained mainly anaerobic bacteria, representative of periodontal microflora, suggesting that periodontal infection in combination with antiresorptive treatment could initiate the osteonecrosis [14].

Treatment choice for MRONJ is still controversial and recommendations from the American Association of Oral and Maxillofacial Surgeons (AAOMS) suggest antibacterial mouth rinses, symptomatic treatment with antibiotics in the early stages and, in more severe cases, superficial debridement for long term palliation of infection and pain [10]. More recent reports suggest a more radical treatment strategy with surgical removal of the necrotic bone and primary closure in combination with antibiotic treatment [15–18] .

Study purpose: To estimate the prevalence of MRONJ in the Region of Skåne and to evaluate the treatment outcome after sequestrectomy versus block resection.

Hypothesis:

a. The prevalence in the Region of Skåne is higher in the prospective study compared with a retrospective from the same region.

b. Block resection is a good treatment method for MRONJ.

c. Co-morbidity is the most important predictor variable when it comes to healing after surgery.

d. The most common initiating factor for development of MRONJ is tooth extraction.

Specific aim: The aims of the present study were to analyse the prevalence and initiating factors for MRONJ and the outcome of surgical therapy, during four years.

MATERIAL AND METHODS

Study design:

To address the research purpose, the investigators designed and implemented a prospective cohort study including two study populations. In Sweden, the health care system has 21 administrative regions. Region Skåne in the south is the third largest, with a population base of approximately 1.3 million people. Four Oral and Maxillofacial Surgery clinics in Skåne (Malmö, Lund, Helsingborg and Kristianstad) are responsible for the treatment of patients with MRONJ. One Maxillofacial Surgeon (FH), working at all of the four departments of Oral and Maxillofacial Surgery during the entire study period, was responsible for the diagnostics, recruitment and treatment of all patients with MRONJ in Skåne. The first study population was composed of all patients presenting for evaluation and management of MRONJ between 1th of January 2012 and 31th of December 2015.

Variables:

Before treatment gender, age, co-morbidity, BP and/or denosumab therapy, dosage and duration until necrosis occurred were recorded in case report form. Initiating factors, site and staging of MRONJ were registered. Intraoral x-rays taken before the tooth extraction by the general dentists referring the patient to hospital were retrieved to analyse the diagnosis initiating MRONJ. A horizontal visual analogue scale (VAS) from 0 to 10 before and after treatment was used to record pain intensity, where zero indicated “no pain” and ten indicated “pain cannot be worse”.

From 1973, inhabitants in Sweden are covered by a health care system and no private insurance is needed; economic reasons for not seeking health care can therefore be ruled out. Referral of patients with suspected MRONJ from general dentists to specialists is a common

and easy procedure. In the region of Skåne there are no private clinics for Oral and Maxillofacial Surgery. It is thus likely that most patients with MRONJ in Skåne have been included during the study period.

To be included in the study sample patients had to be referred to one of the Oral and Maxillofacial Surgery clinics in Skåne. The outcome variable was healing after 2 months after treatment.

Prevalence

The population in the region of Skåne is approximately 1.3 million inhabitants (2012: 1,263,088 inhabitants, 2015: 1,301,316 inhabitants) (*www.skatteverket.se*). Data on the use of BPs and denosumab in the region of Skåne during the period 2012-2015 were obtained from statistics on prescriptions and statistics of drugs delivered to the health care sector in the region (*www.socialstyrelsen.se*), served as the second study population.

MRONJ was diagnosed as defined by the AAOMS, ”as exposed bone in the maxillofacial region over a period of eight weeks, current or previous treatment with bisphosphonates or denosumab, no prior history of radiation therapy to the jaws” [10].

Site

The location of the necrosis was defined as described by Rocha et al. [19] where the jaw bones were divided into right posterior maxilla (segment 1), anterior maxilla (segment 2), left posterior maxilla (segment 3), left posterior mandible (segment 4), anterior mandible (segment 5), and right posterior mandible (segment 6) using the distal surface of the canines as reference.

Staging

The staging of the disease was stage 0-3 according to the recommendations of the AAOMS 2014 [10]. Stage 0 was defined as no clinical evidence of necrotic bone but non-specific clinical findings, radiographic changes and symptoms; Stage 1 as exposed necrotic bone or fistulas that could be probed to bone without pain or signs of infection (asymptomatic); Stage 2 as exposed necrotic bone or fistulas that could be probed to bone with pain or signs of infection (symptomatic) and Stage 3 as exposed necrotic bone or fistulas that could be probed to bone with pain or signs of infection and one or more of the following: pathological fracture, oral-cutaneous fistula, involvement of the maxillary sinus or necrosis extending to the inferior border of the ramus of the mandible.

Histological analysis

Surgical bone specimens were analysed by an oral pathologist (GW) to confirm MRONJ and to rule out concurrent metastatic jawbone disease [20].

Medical treatment

All patients were treated with antibiotics for ten days in relation to the surgical treatment starting two days preoperatively. The antibiotic treatment was carried out with phenoxymethylpenicillin or clindamycin *per os* in case of allergy to phenoxymethylpenicillin.

Following consultation with the patient's oncologist, each patient continued BPs or denosumab medication during the period of surgical treatment unless a break was recommended by the oncologist. For patients undergoing cancer treatment, antiresorptive treatment was an important part of the disease management and necessary for prolonging survival.

Patients were classified into two groups according to surgical treatment:

Surgical treatment

Sequestrectomy: Patients without progressive bone disease with ongoing bone destruction but with a well-defined sequestrum were treated with a local mucosal flap, removal of the sequestrum, debridement of the necrotic bone and closure in one layer with Vicryl 3-0 sutures.

Block resection: In patients with progressive bone disease with ongoing bone destruction, observed on radiograph or ongoing pain and infection, surgical removal of the necrotic bone and primary closure was performed.

Surgical marginal block resection (Fig. 1.) included thorough surgical debridement with saucerisation of the bone until the vital bleeding bone margins were reached (Fig. 2). Primary closure was obtained with Vicryl 3-0 sutures in layers, leaving no dead space.

Healing

The term "healed" was used to describe complete disappearance of exposed bone and the absence of infection in the jaw affected by MRONJ. "Remission": improvement resulting in reduced area of exposed bone, healthy surrounding mucosa, reduced staging and no symptoms (VAS=0). Patients were examined after one week and then at monthly intervals until three months postoperatively. They were then followed-up every three months and asked to contact the clinic if they felt that they had any problems between these appointments. Panoramic radiographs (PR) or, when PR did not provide sufficient view of the surgical area, cone-beam computer tomography was taken one year after the surgical treatment.

Ethical approval was given by the Ethical Review Board in Lund, Sweden, (Dnr 2012/760). The study was conducted in compliance with the Helsinki Declaration and each patient in the project signed a detailed informed consent form.

STATISTICAL METHODS

SPSS for Windows software (Version 14;0 SPSS, Chicago, IL, USA) was used for data management and statistical analysis. Data were analysed using Fisher´s Exact test. A significance level of 5% was used in all tests.

RESULTS

Fifty-five patients with MRONJ were recruited. Forty-three were women (mean age 73.1 years) and 12 were men (mean age 63.6 years). The most common underlying disease was osteoporosis 56% (n=31), followed by breast cancer 20% (n=11), prostate cancer 11% (n=6), multiple myeloma 9% (n=5), lung carcinoma 2% (n=1) and giant cell carcinoma 2% (n=1). Fifty patients were included in the study and followed up for periods of 2-46 months (mean = 15.9 months). Five patients were excluded either since that the patients died or progression of their due diseases making it impossible for them to attend a follow up visit after 2 months.

There were no significant differences (p=0.176) in healing in relation to the underlying disease (Table 1).

Prevalence

The estimated number of patients on oral BPs for treatment of osteoporosis, alendronic acid and risedronic acid, during the period 2012-2015 was around 50 000 in Region Skåne. The prevalence of MRONJ for patients on oral BPs was estimated to be 0.043%.

We estimated that around 700 patients were on intravenous BPs due to metastatic diseases, zoledronic acid and pamidronic acid, during the period 2012-2015 in Region Skåne. The prevalence of MRONJ in patients on intravenous bisphosphonates was estimated to be 1.03%.

The estimated numbers of patients on high dose denosumab, due to metastatic diseases during the period 2012-2015 in Region Skåne were around 1700. The prevalence of MRONJ in patients on denosumab was estimated to be 3.64%.

Oral BPs

Twenty-five patients were treated with oral BPs. Twenty-one patients had monthly alendronic acid 70 mg, three patients received ibandronic acid 50 mg/day and one patient had risedronic acid 35 mg/week.

The mean treatment time with oral BPs before development of MRONJ was 70.5 months (range 25-180 months). The mean accumulated dose was 4503 mg alendronic acid, 156 000 mg ibandronatic acid and 3395 mg risedronic acid before development of MRONJ.

Intravenous BPs

Seven patients were treated with intravenous BPs, four patients with zoledronic acid 4 mg/month and three patients with pamidronic acid 90 mg/month.

The mean treatment time with zoledronic acid before development of MRONJ was 30.0 months (range 10-65 months) and the mean accumulated dose was 150 mg. The mean treatment time with pamidronic acid before development of MRONJ was 18.0 months (range 5-24 months) and the mean accumulated dose was 1620 mg.

Denosumab

Eleven patients were treated with 120 mg subcutaneously administered denosumab once a month. The mean treatment time before development of MRONJ was 15.8 months (range 6-41 months). One patient was treated with a 60 mg subcutaneously administered denosumab twice a year. Treatment time before development of MRONJ was 17.0 months. The mean accumulated dose of denosumab given before development of MRONJ was 1740 mg.

Combination of oral BPs, intravenous BPs and/or denosumab

Eleven patients were treated with a combination of oral and/or intravenous BPs and/or denosumab.

Five patients were treated with monthly oral BPs, four with alendronic acid 70 mg and one with risedronic acid 35 mg and subsequently switched to 60 mg subcutaneously administered denosumab twice a year. The mean treatment time with oral BPs in combination with denosumab before development of MRONJ was 84 months (range 40-106 months).

Three patients were treated with monthly oral BPs, two with alendronic acid 70 mg and one with risedronic acid 35 mg and then switched to an annual 5 mg infusion with zoledronic acid. The mean duration of anti-resorptive treatment was 83 months (range 48-89 months) before development of MRONJ.

Two patients were treated with intravenous BPs, zoledronic acid 4 mg/month and then switched to 120 mg/month subcutaneously administered denosumab. The mean duration of antiresorptive treatment was 61 months (range 56-66 months) before development of MRONJ.

One patient was treated with intravenous BPs, zoledronic acid 4 mg/month and then switched to orally administered ibandronic acid 50 mg/day. The total duration of antiresorptive treatment before development of MRONJ was 89 months.

Site

Most lesions were located in the mandible 75% (n=41) with 32 in the posterior part (segment 4 or 6), five in the anterior part and four cases were located in more than one segment of the mandible.

Fourteen (25%) lesions were located in the maxilla, 11 in the posterior part, two in the anterior part and one involved more than one segment of the maxilla.

There were no significant differences (p=0.156) in healing in relation to the location of the necrosis (Table 2).

Stage

Ten patients were referred to as Stage 1, 36 patients were classified as Stage 2, and nine patients as Stage 3.

There were no significant differences (p=0.067) in healing in relation to the stage of the necrosis (Table 4).

Initiating factor

The most common initiating factor for development of MRONJ were tooth extraction in 39 patients; 10 cases due to marginal periodontitis; 3 occurred spontaneously; 2 due to apical periodontitis and one after denture trauma.

In 32 out of 39 cases the initiating factor was tooth extraction; it was possible to retrieve from general dental practitioner the intraoral radiographs from before the extraction. These were analysed by a specialist in Oral and Maxillofacial Radiology. Twenty-nine (91%) of the 32 tooth extractions were of teeth with either severe marginal periodontitis (15 patients) or apical periodontitis (3 patients) or both diagnoses on the same tooth (11 patients). Together with the ten patients of MRONJ caused by marginal periodontitis and the two due to apical periodontitis alone as an initiating factor, local periodontal destruction including marginal bone loss adjacent to root surfaces preceded development of MRONJ in a total of 41 patients.

Histological analysis

The histological analysis of resected bone confirmed the diagnosis MRONJ without sign of metastasis or tumours in all cases. All specimens showed necrotic fragments of bone with extensive resorption of the trabecular surfaces. Most often, marrow spaces were filled with bacteria along with the granulation tissue. In addition, slender cords of squamous epithelium sometimes covered the bone surfaces. Occasionally, there were signs of previous bone apposition (Fig. 4). The resection samples showed no signs of metastatic jawbone disease.

Surgical treatment

Sequestrectomy

Ten patients were treated with sequestrectomy. Five lesions (50%) healed (Table 4). Three went into remission (two patients with stage 2 and one with stage 3). The overall improvement rate was 8/10 (80.0%).

Mean follow-up time was 13.3 months (range 5-29 months). After healing, no adverse events were recorded.

Block resection

Forty patients were treated with block resection.

Thirty-one lesions healed (77.5%) (Table 4). Six cases went in remission (four patients with stage 2 and two with stage 3). The overall improvement rate was 37/40 (92.5%)

Mean follow-up time was 16.7 months (range 2-46 months). After healing, no adverse events were recorded.

There were no difference (p=0.118) in healing in patients treated surgically with block resection or sequestrectomy (Table 4).

There were no difference (p=0.094) in healing rate between men or women (Table 5).

Pain intensity

Mean VAS for ten patients treated with sequestrectomy before treatment, 3.9 and after treatment, 1.0. Mean VAS for 40 patients treated with block resection before treatment, 3.8 and after treatment, 0.2. Mean VAS for six patients in remission before treatment, 3.7 and after treatment, 0.0.

DISCUSSION

Probably most cases in Skåne of MRONJ from the period of 2012-2015 have been included in this study. Those few not included might be patients not seeking health care due to asymptomatic lesions and we therefore estimate that around 90% have been included. In a retrospective study [11] including patients from the same health care region (Skåne), the same number of patients (n=55) with MRONJ was identified, but with an inclusion period of eight years compared with the four years in the present prospective study. This further supports the hypothesis that the drop outs are few.

To our knowledge, this is the first study that reports the condition of the extracted teeth that leads to MRONJ. The finding that periodontal disease preceded tooth extraction and probably initiates the development of MRONJ in most cases in the study, highlights the need for a dental examination before commencing antiresorptive treatment. This might reduce and prevent the number of patients who develop MRONJ and further supports data from our previous study that the necrotic bone contains mainly anaerobic bacteria, representative for periodontal microflora, suggesting that a periodontal infection in combination with antiresorptive treatment initiate the osteonecrosis [14].

Our results confirm data from a previous retrospective study from the same region showing the prevalence of MRONJ to be much lower in patients on oral BPs due to osteoporosis than patients treated with intravenous BPs due to metastatic disease [11]. This Swedish study reports a relatively low prevalence of MRONJ in comparison with studies from other countries showing higher prevalence [12]. This might be explained by the decreasing number of individuals with marginal bone loss and periodontitis in Sweden since the general dental insurance was introduced in 1973 [21].

A standard therapy has not yet been established for MRONJ and surgery has previously been reported to be capable of exacerbating bone exposure [22–24]. Treatment recommendations by AAOMS indicate that conservative therapies could be applied to Stage 1 and Stage 2 MRONJ and that surgical procedure may be unnecessary [10] . This is in contrast to the results in the present study were healing after block resection of MRONJ occurred in 3 out of 4 patients, compared with sequestrectomy were only half of the patients healed. Based on our results, we recommend that block resection should be used as the treatment of choice. In a previous study [11], only 26% of the group of patients with metastatic disease healed after treatment with sequestrectomy.

In most publications, the treatment goal for MRONJ healing is defined as no signs of exposed necrotic bone after treatment and complete mucosal coverage. In the present study, 72% of the lesions healed completely. However, for the patients, especially those with metastatic disease, palliation as a treatment goal is probably sufficient. In our study, another six (11%) patients went into remission without subjective symptoms but with some remaining exposed bone, after block resection in combination with oral antibiotics. These patients were not willing to undergo additional surgery, suggesting that had been successfully treated, now being classified as stage 1 instead of stage 2 or 3 as before treatment.

Our success rate for patients treated with block surgery is in accordance with other studies [15,17,25]. A recent study showed that periopathogenic bacteria are present in visually healthy bone adjacent to the necrotic bone [14]. Better healing with block resection than sequestrectomy might thus be explained by the fact that all infected bone was removed.

Even more radical surgical approaches with coverage of sinus communication after surgical removal of necrotic bone with the buccal fat pad [26] or in the mandible with a myofascial flap [27] might have resulted in a higher success rate in combination with block resection. However, in the present study none of the patients with unhealed lesions after surgery were interested in

a second surgical intervention. In stage 3, immediate reconstruction with vascularized graft was considered an option. However, the operation was not possible due to the patients due disease.

Based on results from a previous study, antibiotics specific for oral microflora [14], phenoxymethylpenicillin was used *per os* for 10 days. The same success rate was obtained when an intravenous broad spectrum antibiotic like sitafloxacin is used [28]. Antibiotics specific for oral microflora, phenoxymethylpenicillin, lowers the risk of developing resistant strains and can therefore be highly recommended.

In patients medicated with oral BPs, the median treatment time was 70.5 months before being diagnosed with MRONJ, similar to data reported by Fung et al. [29]. In our study, we also found a tendency, not statistically verified, for MRONJ to appear earlier in patients treated with high dose denosumab (15.8 months) compared with zoledronic acid (30.0 months). Further studies are needed to confirm these results.

Although MRONJ is a serious complication to BPs and denosumab treatment, the benefits of the medication on due disease and life quality predominates. Instead of stopping the antiresorptive treatment, a drug holiday before tooth extraction, if possible, might further reduce the number of patients developing MRONJ [10], especially for patients on denosumab with a much shorter half-life compared with BPs.

We regard the risk of bias in our present prospective study as relatively low since drop-outs were few due to the Swedish health care system. The patients were also consecutively recruited and treated by the same surgeon. A limitation is that a control group could not be included, due to ethical considerations.

CONCLUSION

The prevalence of MRONJ in Sweden is low. Periodontitis is the most common initiating factor. The treatment outcome of MRONJ demonstrates healing in most patients treated surgically. Our data suggest that treatment with BPs and denosumab can be carried out with relatively low risk of MRONJ.

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CONFLICT OF INTEREST

None to declare

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Fig. 1: MRONJ caused by denosumab in the left posterior maxilla (Segment 3) in a 63 year old woman with breast cancer treated with block resection; Panoramic radiograph before (A) and after treatment (B).

Fig. 2: Stage 2 MRONJ located in the anterior mandible in a 66 year old woman with breast cancer, treated with denosumab for 13 months (A). Block resection of the MRONJ lesion until the vital bleeding bone margins were reached and smoothing of sharp edges (B). Healing at follow-up ten months postoperatively (C).

Fig. 3: Flow-chart describing the inclusion and treatment process of the patients.

Fig. 4: Bone specimen from 76 year-old woman treated with alendronate for 70 months due to osteoporosis. Section shows necrotic bone with signs of recent bone apposition (arrows) and resorption. Fragments of squamous epithelium (A) and bacteria (B) have replaced the original bone marrow. Hematoxylin & eosin stain; original magnification 40 ×.

Table 1. Healing in relation to the co-morbidities osteoporosis and cancer.

			Outcome		
			Healed	Failed	Total
Co-morbidities	Osteoporosis	Count	23	6	29
		%	79,3%	20,7%	100,0%
	Cancer	Count	13	8	21
		%	61,9%	38,1%	100,0%
Total		Count	36	14	50
		%	72,0%	28,0%	100,0%

Table 2. Healing in relation to the site of the necrosis.

			Outcome		
			Healed	Failed	Total
Site	1 or 3	Count	8	2	10
		%	80,0%	20,0%	100,0%
	2	Count	2	0	2
		%	100,0%	0,0%	100,0%
	Whole upper jaw	Count	0	1	1
		%	0,0%	100,0%	100,0%
	4 or 6	Count	22	6	28
		%	78,6%	21,4%	100,0%
	5	Count	2	3	5
		%	40,0%	60,0%	100,0%
	Whole lower jaw	Count	2	2	4
		%	50,0%	50,0%	100,0%
Total		Count	36	14	50
		%	72,0%	28,0%	100,0%

Table 3. Healing in relation to the stage of the necrosis.

			Outcome		
			Healed	Failed	Total
Stage	1	Count	7	1	8
		%	87,5%	12,5%	100,0%
	2	Count	26	8	34
		%	76,5%	23,5%	100,0%
	3	Count	3	5	8
		%	37,5%	62,5%	100,0%
Total		Count	36	14	50
		%	72,0%	28,0%	100,0%

Table 4. Healing in relation to surgically treatment with block resection versus sequestrectomy.

			Outcome		
			Healed	Failed	Total
Surgical treatment	Seques ect	Count	5	5	10
		%	50,0%	50,0%	100,0%
	Block resec	Count	31	9	40
		%	77,5%	22,5%	100,0%
Total		Count	36	14	50
		%	72,0%	28,0%	100,0%

Table 5. Healing in relation to gender.

			Outcome		
			Healed	Failed	Total
Gender	Male	Count	4	5	9
		%	44,4%	55,6%	100,0%
	Female	Count	32	9	41
		%	78,0%	22,0%	100,0%
Total		Count	36	14	50
		%	72,0%	28,0%	100,0%