ABSTRACT

Objective: Verifying the evidence of therapeutic efficacy in the topical application of metronidazole for controlling wound odor. Methods: A systematic literature review, according to the Cochrane Collaboration recommendations. Results: 329 articles were identified in the Cochrane, LILACS, SciELO, CINAHL and PubMed databases, with 14 of them being included in the final sample. Two of the studies were double-blind randomized clinical trial studies. Conclusion: The actual effectiveness of metronidazole in controlling wound odor cannot yet be evidenced due to the absence of strong evidence from studies on the subject, despite clinical practice recommending its benefits.

DESCRIPTORS
Wounds and Injuries; Deodorization; Metronidazole; Wound Infection; Review.
INTRODUCTION

Colonization and bacterial infection are factors that interfere with wound healing, especially in chronic wounds. To control these factors, anti-septics and topical antibiotics are accepted as the best option for local infection treatment (in some cases the use of systemic antibiotics is necessary). Infection in wounds slows the healing process and may have systemic complications if not quickly controlled(1).

Unpleasant odor is a common and distressing concern for people with infected wounds, as well as for their family members and caregivers. Patients with fetid wounds often experience social isolation, depression, shame, embarrassment and lack of appetite, factors that can have a negative impact on their quality of life. Nurses who treat these patients face difficult clinical challenges when treating the cause and controlling the symptoms(2).

Wound odor is not only experienced by patients under palliative care, it is also perceived in chronic leg wounds and pressure ulcers. Wound necrosis contributes to the occurrence of odor, but it cannot be perceived as the main cause of its emergence(3).

There are several silver-based, iodine-based, honey-based and topical antibiotic products available to help odor control. Among topical antibiotics, metronidazole has been described as effective in controlling wound odor. Metronidazole is a nitroimidazole derivative with antimicrobial action. It also has bactericidal activity against gram-negative anaerobic bacilli, all sporulated anaerobic cocci and gram-positive bacilli. Putrid odor is characteristic of local infection by anaerobic bacteria, which justifies its action and use for odor control(4).

Thus, we aimed to verify the evidence of therapeutic efficacy in using topical metronidazole for controlling wound odor.

METHOD

We performed a systematic literature review (SR) on the use of metronidazole as topical wound therapy for odor control of any etiology according to the recommendations of the Cochrane Collaboration(5). For this purpose, we included studies published in the Cochrane, LILACS, CI-NAHAL, SciELO and PubMed databases, until December 2014. Descriptors indexed on MeSH and DeCS databases, two different researchers individually analyzed studies recovered by databases. After searching the databases, two different researchers individually analyzed the retrieved articles (by title and abstract) and identified articles relevant to the proposed theme – metronidazole in wounds. Studies to be read in full and those which were not sufficient, studies were included in pre-selection, thereby avoiding erroneous deletions. After the studies were obtained in full, they had their references checked, in order to recover possible studies not yet verified. Data were collected during full article readings, through a specific instrument containing: title, journal, year, main author, type of study, solution used.

Data were analyzed in three stages:

**Phase 1 – Characterization of the selection process of studies:** analysis of data concerning the total number of studies recovered by databases. After searching the databases, two different researchers individually analyzed the retrieved articles (by title and abstract) and identified articles relevant to the proposed theme – metronidazole in wounds. Studies to be read in full and those which would be included in the SR were selected by consensus.

**Phase 2 – Characterization of included studies:** analysis of data related to included studies by two researchers, such as title, journal, year, main author, study type, application method, concentration of metronidazole and outcome.

**Phase 3 – Quality assessment and evidence of the included studies:** studies had their quality (internal validity) assessed according to STROBE – Strengthening the Reporting of Observational Studies in Epidemiology for observational studies(6) and CONSORT – Consolidated Standards of Reporting Trials for clinical trials(6) (case reports do not have internal quality evaluation).

For STROBE evaluation, each of the 22 criteria received a score from 0 to 1 (0 - described and 1 - not described). For evaluation according to CONSORT, also consisting of 22 items, scores were performed considering 0 - not described, 1 - partially described and appropriate and 2 - appropriate (in cases where not applicable, such as in uncontrolled clinical studies, items were not added). The total score was converted into percentages for better
article evaluation. Items that reached a percentage higher than 70% were considered of good quality.

RESULTS

Research showed that there were no systematic reviews on the use of metronidazole in wound odor control. 26 studies were pre-selected, one study in animals and 6 studies performed by other means of administration of metronidazole (three orally, one intravenously and two studies did not describe the method of administration) and four review studies were excluded (Figure 1). Among the three letters to the editor identified, one describes a randomized clinical trial, but there was not enough data for study evaluation, so it was then deleted. 14 articles were included in the study (Chart 1).

![Table and Figure]

Figure 1 – Description of the strategy carried out for the search and inclusion of articles – São Paulo, SP, Brazil, 2015.

Chart 1 – Description of the 14 studies identified on the use of metronidazole in wounds for odor control – São Paulo, SP, Brazil, 2015.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Sample</th>
<th>Intervention</th>
<th>Application</th>
<th>Wound type</th>
<th>Outcome for odor control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashford, 1980(9)</td>
<td>1 patient. Randomized, double-blind case study.</td>
<td>Metronidazole 200 mg 3 times a day.</td>
<td>Does not describe administration and application.</td>
<td>Malignant neoplastic wound.</td>
<td>Experimental group had odor reduction (p&lt;0.01), and reduction of microbial load (p &lt; 0.005). CONSORT: 42%</td>
</tr>
<tr>
<td>Gomolin, 1983(10)</td>
<td>4 patients</td>
<td>Metronidazole 1% solution.</td>
<td>Moisten gauze, changed every 8h.</td>
<td>Pressure ulcers in stages II to IV.</td>
<td>Odor reduction from 48 hours to 1 week.</td>
</tr>
<tr>
<td>Pierleoni, 1984(11)</td>
<td>2 patients</td>
<td>Metronidazole 1% solution.</td>
<td>Moisten gauze, changed every 8h.</td>
<td>Pressure ulcers in stages III and IV.</td>
<td>High reduction in odor control.</td>
</tr>
<tr>
<td>Burnakis, 1989(12)</td>
<td>1 patient</td>
<td>Metronidazole 1% solution, autoclaved at 121°C for 20 minutes.</td>
<td>10 ml of solution was applied to gauze at each shift. After the gauze dried, it was removed, &quot;warm light&quot; was applied for 20 to 30 minutes.</td>
<td>Pressure ulcer (stage was not described).</td>
<td>Odor reduction in 24 to 48 hours.</td>
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continued...
Controlling wound odor with metronidazole: a systematic review

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<tr>
<td>Witkowski1, 1991(13)</td>
<td>10 patients</td>
<td>Metronidazole gel (without description of concentration)</td>
<td>Soak with saline solution, application of a thin layer of gel covered with gauze. Changed every 12 hours.</td>
<td>Sacral pressure ulcer stages III to IV.</td>
<td>Odor elimination of all wounds in 36 hours. - No statistical results. STROBE: 46%</td>
</tr>
<tr>
<td>McMullen, 1992(14)</td>
<td>11 patients</td>
<td>Metronidazole 0.75% gel in wounds and 1% solution for fistulas</td>
<td>Applied 1 or 2 times a day.</td>
<td>Malignant neoplastic wound, Radiodermatitis, fistula and pressure ulcer.</td>
<td>After 24 hours the odor was noticed only at handage opening/removal; in 5 days odor was eliminated. - No statistical results. STROBE: 61%</td>
</tr>
<tr>
<td>Newman, 1989(15)</td>
<td>68 patients</td>
<td>Metronidazole 0.8% gel</td>
<td>Application of metronidazole gel covered with gauze. Changed once a day.</td>
<td>Not described, only mentions that wounds are fetid.</td>
<td>Odor reduction in 96% of the subjects, where 50% were total control and 46% were partial control. - No statistical results. CONSORT: 62%</td>
</tr>
<tr>
<td>Bower, 1992(16)</td>
<td>9 patients</td>
<td>Comparison of two groups: metronidazole 0.8% gel versus placebo.</td>
<td>Placebo or metronidazole gel applied once a day for 5 days, followed by 6 days of metronidazole.</td>
<td>Malignant neoplastic wound.</td>
<td>Odor reduction in 5 days for experimental group (p &lt; 0.001). CONSORT: 71%</td>
</tr>
<tr>
<td>Finlay, 1996(17)</td>
<td>39 patients</td>
<td>Metronidazole 0.75% gel.</td>
<td>Application of gauze with metronidazole gel.</td>
<td>Neoplastic wounds and leg ulcers.</td>
<td>Odor reduction with metronidazole (p &lt; 0.002). CONSORT: 84%</td>
</tr>
<tr>
<td>Kuge, 1996(18)</td>
<td>5 patients</td>
<td>Comparison of two groups: metronidazole 0.8% gel versus placebo.</td>
<td>Applied 1 or 2 times a day.</td>
<td>Wounds caused by breast cancer.</td>
<td>Odor reduction or elimination from 2 to 5 days in the experimental group. - No statistical results. CONSORT: 65%</td>
</tr>
<tr>
<td>Bale, 2004(19)</td>
<td>41 patients</td>
<td>Comparison of two groups: metronidazole 0.8% gel versus placebo.</td>
<td>1 application once a day.</td>
<td>Arterial, venous, dehiscence and pressure ulcer.</td>
<td>100% reduction for group with metronidazole versus 76% placebo (p&lt;0.05). CONSORT: 68%</td>
</tr>
<tr>
<td>Kalinski, 2005(20)</td>
<td>16 patients</td>
<td>Metronidazole 0.75% gel.</td>
<td>Applied 1 or 2 times a day.</td>
<td>Neoplastic wounds.</td>
<td>100% odor reduction. CONSORT: 73%</td>
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</table>

DISCUSSION

In 1978(7), one study reported (in the form of a letter to the editor) the putrid odor that some pressure ulcers exuded and other cases in which patients progressed to sepsis caused by anaerobic bacteria. The authors describe that from previous publications on the successful treatment of patients with sepsis caused by anaerobic bacteria through systemic metronidazole, they began to suggest its topical use on infected wounds. In the same report, the authors mention that there was a lack of topical formulations at that time, therefore the hospital pharmacy manipulated a metronidazole 1% solution, and applied it to pressure ulcers, diabetic ulcers, leg ulcers and venous ulcers with odor, through moistened gauze. As the outcome, there was odor reduction from the wounds within a few hours, in addition to there being negative cultures on the surface of the wounds after 24 hours.

In 1980, other authors(8) proposed the use of metronidazole for odor control in neoplastic wounds for the first time, to publish a case report in which the wound had offensive and putrid odor – characteristic of infection by anaerobes. They proposed a local treatment with 200 mg of metronidazole three times a day, with no description of the form of administration (oral, intravenous or topical). They found odor reduction in a week, which they only noticed when they removed the dressing and it was less offensive than before. According to the authors, the patient returned to work as a teacher, noting that this would be unlikely in the previous condition, improving their quality of life and without any toxicity.

Currently, topical metronidazole is recommended for wounds to control odor through its action on anaerobic bacteria responsible for producing volatile acids, which cause the odor, without the side effects of oral use(19). Topical application of metronidazole has little or no systemic absorption(20).

According to this review, topical wound therapy uses metronidazole solution in 0.75 and 0.8%, in the form of a gel or liquid. However, some authors describe its application
by macerating oral tablets with subsequent dilution; others only describe that it was manipulated without detailing how this was done, and others describe the use of Metrotop® (metronidazole 0.8% gel not available in Brazil). No instruments for the evaluation of odor have been identified, which compromises the interpretation of results when this is described as odor reduction.

Despite being identified in only two randomized clinical trials on topical metronidazole therapy for wounds, the results showed different outcomes (making it impossible to conduct meta-analysis). Clinical experience suggests that metronidazole is effective in odor control, especially in neoplastic (cancer) wounds.

In Brazil, metronidazole is available in the form of vaginal cream (8% - 400mg/5g and 10% - 500mg/5g), oral suspension (40mg/ml), oral tablets/pills (250mg or 400mg) and parenteral solution (0.5%). Topical formulations have high concentration because the amount of cream/ointment applied is small, about 5 to 10g in the treatment of vaginitis or acne rosacea.

Two Brazilian oncology hospitals report using pills diluted in saline solution at bedside in their protocols for odor control of neoplastic wounds; and silver and papain are used for odor control of other etiologies.

Because there are no ready-made metronidazole 0.8% topical formulations, manipulation becomes necessary – for example metronidazole tablets associated to physiological saline solution (off-label use).

CONCLUSION

Based on the results of this systematic review, the metronidazole solution is recommended in clinical practice to control odor in infected wounds, and used more appropriately in malignant neoplastic wounds, but there are no randomized controlled trials of strong evidence to effectively support this. Other clinical studies of stronger evidence should be performed so we can use off-label metronidazole more assertively and clinically safe.

REFERENCES