The Use of Octenidine Dihydrochloride in the Treatment of Musculoskeletal Infections

Zastosowanie dihydrochlorku oktenidyny w leczeniu zakażeń narządów ruchu

Abstract

Background. The treatment of musculoskeletal infections is a great therapeutic challenge for orthopedists and microbiologists due to antimicrobials' limited penetration of the musculoskeletal tissues and biofilm formation on endoprostheses and wounds. These problems motivated the authors to investigate the efficacy of octenidine dihydrochloride in the treatment of patients with musculoskeletal infections.

Objectives. To evaluate the efficacy of octenidine in the local treatment of osteoarticular infections, including long-term observation of the infected regions and monitoring of any recurrence of the inflammatory process.

Material and Methods. The study involved eight patients who had undergone surgery at the Orthopedics and Musculoskeletal Trauma Ward of the Specialist Hospital in Kościerzyna, Poland. Irrigation-drainage was used at the surgical site and swabs soaked with antiseptic were applied. Microbiologic techniques were used to assess the antimicrobial efficacy of octenidine.

Results. Microorganisms were eradicated in all the patients in the study, and during the 30 months of observation, no recurrence of the inflammatory process was observed.


Key words: musculoskeletal infection, octenidine dihydrochloride, biofilm.
Musculoskeletal infections still cause considerable problems in the treatment of orthopedic patients. The frequency of such infections ranges from 0.5% to 10%, depending on the type, the length and scope of the operation and on any perioperative antibiotic prophylaxis used [1]. The type of implant, the age of the patient and coexisting illnesses (e.g. diabetes, diminished resistance) are also among the factors affecting the risk of infection and the healing process [2].

The main etiological factors in musculoskeletal infections are most often microorganisms that inhabit the skin and mucous membranes of the hospital staff and/or the patients themselves (endogenous infections). Hospital equipment (tools, implants, drains etc.) and the hospital environment (carts, desks, shelves, etc.) are also considered a major source of infections [3]. Staphylococci that are part of the physiological flora of skin, such as Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus auricularis and other coagulase-negative staphylococci (CNS) are among the most frequent etiological factors in musculoskeletal infections. Coagulase-positive Staphylococcus aureus – part of physiological flora of 25% to 30% of the healthy population – is another important cause of infection among orthopedic patients. G(−) bacilli are an etiological factor in 35% of musculoskeletal infections [1].

These infections begin during the operation or implantation procedure with nonspecific sedimentation of bacteria, followed by adhesion to the prosthetic surface. Colonization and accumulation then takes place, and the next step in the process is the formation of a multi-layer biofilm structure on the surface of the tissue or prosthesis [4].

Biofilm protects bacterial cells from specific and nonspecific host resistance mechanisms. It hinders phagocytosis, opsonization and chemotaxis; blocks the blastogenesis of T and B cells; and hinders the penetration of antibodies and antibiotics [5].

Bacteria in the deeper layers of biofilm display a slower metabolic rate and a higher resistance to antibiotics and antiseptics, which is reflected in their higher virulence [6]. At present, despite the introduction of implants coated with various substances, there is no surface that is completely resistant to bacterial adhesion and biofilm formation. The treatment of musculoskeletal infections is therefore a great therapeutic challenge for orthopedists and microbiologists.

Another challenge is the nature of the blood supply to the bones and soft tissues of the musculoskeletal system, which limits the penetration of antibiotics. Moreover, even new generations of antibiotics are ineffective against antibiotic-resistant microorganisms [7]. These difficulties with antibiotherapy prompted the authors of this study to consider the use of antiseptics as efficient local antimicrobials in the treatment of musculoskeletal infections.

According to consensus on the use of antiseptics on wounds [8], an antiseptic should have a broad spectrum of effectiveness and rapid onset of action, should ensure protection from contamination, should be well tolerated by all types of skin and mucous membranes, should not have any toxic effects and – last but not least – should not interfere with the natural process of wound healing.

Octenidine dihydrochloride, commonly known as octenidine, is one of the antiseptics that displays all of these features. It is a cationic antimicrobial substance that is strongly adsorbed onto negative cell surfaces and reacts with the polysaccharides in microorganisms’ cell walls. This leads to leakage of the cytoplasmic membrane, disturbing the enzymatic systems and mitochondria. Octenidine displays a broad spectrum of effectiveness against both Gram-positive and Gram-negative bacteria (including chlamydiae) and fungi, and at the same time exhibits low cytotoxicity. A unique property of this antiseptic is its ability to form complexes with eukaryotic cells and still maintain antimicrobial effectiveness [9]. This might enhance its tolerability, because only the top cell layer is exposed to the active substance, which is released again into the surrounding area in low, non-cytotoxic concentrations from the complexes that are formed and thus continues to be bioavailable.

Octenidine is approved as a medicinal substance for skin, mucous membrane and wound antisepsis. For antisepsis, it is used either alone or in combination with phenoxethanol or aliphatic alcohols. Combining octenidine with ethanol (2–10%) and organic acid (0.5–2%) further improves its tolerability and efficacy [10]. Overall, octenidine-based wound antiseptics should be regarded as the agent of choice for infected acute wounds; in appropriate concentrations they are also suitable for the treatment of infected chronic wounds.

These advantages motivated the authors’ investigation of the efficacy of octenidine in treating patients with musculoskeletal infections. They aimed at: evaluating the efficacy of octenidine in the local treatment of osteoarticular infections; evaluating the sensitivity of microorganisms to octenidine under in vivo conditions; performing long-term observation of the infected regions and monitoring of any recurrence of the inflammatory process.

Material and Methods

The study involved eight patients at the Orthopedics and Musculoskeletal Trauma Ward of
the Specialist Hospital in Kosciernyna, Poland. All the patients were experiencing bacterial inflammation of the musculoskeletal system, and antibiotic therapy had failed to offer satisfactory results. This led to the switch from antibiotherapy to treatment with octenidine. The patients were from 26 to 81 years of age, with an average age of 61 years (26–81 years). The ratio of females to males was 50 : 50. The average length of hospitalization was 83.8 days (21–267 days). 87.5% of the patients had previously been hospitalized because of earlier musculoskeletal infections. Among these, 28.5% had been hospitalized more than twice.

**The Patients’ Characteristics**

In three cases the diagnosis was purulent inflammation of the hip joint following endoprosthesis implantation. In two patients, the inflammatory process had developed as a result of fractures (in one case, a compound fracture of left femur; in the other, a fracture of the right shin with subsequent purulent inflammation of the tibia). Two patients suffered from osteoarthritis without any earlier fracture or endoprosthesis implantation (one case was acute chronic hematogenous inflammation of the left thigh; the other was purulent inflammation of the shinbone resulting from a gunshot wound in 1944). In the case of one female patient, temporary inflammation of the hip joint developed after alloplastic surgery performed to treat a congenital dislocation of the hip joint.

Before the alloplasty, distraction was performed to move the dislocated joint 12 cm in the distal direction, which permitted the endoprosthesis to be implanted at the level of the anatomical acetabulum.

**Treatment with Octenidine**

Local treatment with octenidine was performed as follows:

Before octenidine use, the wound was debrided to evacuate necrotic tissue and any pus, and to remove any infected implant and/or bone cement. The infected wound was rinsed with a 1 : 1 solution of octenidine and water. The antiseptic solution remained in the marrow canal or wound for 2–5 minutes of contact time. This specific contact time was chosen to avoid any cytotoxic effect of the antiseptic on the tissue [10]. The antiseptic solution was subsequently removed and the wound was rinsed with water for injections (aqua pro injectione).

In the postoperative period, the antiseptic solution was administered once a day using irrigation-drainage. The antiseptic solution was left for 2–5 minutes, and then was rinsed off using 500 ml of water for injections.

During period of irrigation-drainage application, local antibiotherapy was not administered and the wound was rinsed with Ringer’s solution, using a total of 2500–3000 ml/day.

In cases of deep surface wounds, swabs soaked with the antiseptic were used locally and the wound was rinsed with water for injections.

The antiseptic solution was used from 8 to 35 days (average 17.9 days); the results of bacteriological cultures served as the indication for continuing or discontinuing the treatment. In all patients, in addition to local therapy, systemic treatment in the form of targeted intravenous antibiotic therapy was also applied.

**Evaluating the Efficacy of the Treatment**

The efficacy of the treatment was evaluated by using microbiological methods to monitor the area where the antiseptic was applied. Materials (swabs, drainage liquid, tissue fragments taken up intraoperatively from the infected area) were collected before rinsing with antiseptic every day.

In the initial period of the experiment, material for microbiological tests was collected from two patients twice a day: before and after antiseptic use.

The material obtained was processed using classic microbiologic techniques. Microorganisms were identified using API tests and the VITEK® automated system. Drug sensitivity was evaluated using the diffusion disk method. The number of cultured microorganisms was estimated using a semi-quantitative method on subsequent isolation sectors of a solid medium (where “-” meant the presence of single colonies on the first isolation culture; “+” meant microorganism growth on the whole surface of the first culture; “+++” meant microorganism growth on the first and second isolation cultures; and “++++” meant microorganism growth on the first, second and third isolation cultures). Material was also cultured in brain-heart broth, and the growth of microorganisms in this medium was analyzed by culturing them on a solid medium.

**Results**

Before octenidine was applied, coagulase-negative staphylococci (CNS) were the dominant etiological factor in five patients’ infections. Mixed infection occurred in two cases (one case was CNS and *Staphylococcus aureus*, the other was CNS and *Enterococcus faecium*). In one patient the etiological factors were *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and CNS. The microorganisms
### Table 1. Outline of the treatment of patients with musculoskeletal infections with octenidine dihydrochloride

<table>
<thead>
<tr>
<th>Initials</th>
<th>Age (Wiek)</th>
<th>Sex (Płeć)</th>
<th>Hospital stay in days (Czas pobytu w szpitalu – dni)</th>
<th>Diagnosis (Rozpoznanie)</th>
<th>Microorganisms isolated during hospitalization (Drobnoustroje wyizolowane podczas leczenia szpitalnego)</th>
<th>Method and duration of octenidine use (Metoda i czas działania oktenidyny)</th>
<th>Result of treatment ( Wynik leczenia)</th>
<th>Long-term observations (Obserwacje odległe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WB</td>
<td>81</td>
<td>M</td>
<td>267</td>
<td>septic loosening of hip endoprosthesis</td>
<td><em>S. aureus</em>, <em>Corynebacterium</em> spp., <em>CNS</em>, <em>E. faecium</em>, <em>S. varneri</em>, <em>E. coli</em>, <em>S. haemoliticus</em>, <em>A. baumanii</em>, <em>S. epidermidis</em>, <em>Bacillus</em> spp.</td>
<td>irrigation-drainage/ wound rinsing with octenidine for 16 days</td>
<td>On the 12th day of treatment the microbiologic cultures became negative and remained so through the end of the treatment</td>
<td>the patient was released to his home. During the next 30 months there was no recurrence of the inflammation process</td>
</tr>
<tr>
<td>KP</td>
<td>26</td>
<td>M</td>
<td>26</td>
<td>multiple injuries incl. compound fracture of the femur</td>
<td><em>E. faecalis</em>, <em>S. aureus</em></td>
<td>irrigation-drainage; on the 3rd day of treatment, switched to octenidine for 16 days</td>
<td>on the 13th day of treatment the microbiologic cultures became negative and remained so through the end of the treatment</td>
<td>the patient was released to his home with the wound healed. During the next 30 months there was no recurrence of the inflammation process</td>
</tr>
<tr>
<td>KM</td>
<td>64</td>
<td>F</td>
<td>161</td>
<td>septic inflammation of hip joint after alloplasty</td>
<td><em>A. baumanii</em>, <em>S. aureus</em>, <em>S. epidermidis</em>, <em>CNS</em>, <em>Pseudostreptococcus</em> spp., <em>Bacillus</em> spp., <em>E. faecalis</em>, <em>S. capitis</em></td>
<td>debridement of inflamed tissue and irrigation-drainage with octenidine for 8 days</td>
<td>after 4 days the microbiologic cultures became negative</td>
<td>the patient was released to her home. During the next 30 months there was no recurrence of the inflammation process</td>
</tr>
<tr>
<td>JK</td>
<td>67</td>
<td>M</td>
<td>24</td>
<td>recurrence of chronic hematogenous inflammation of the femur</td>
<td><em>S. aureus</em>, <em>E. faecalis</em>, <em>CNS</em> (–)</td>
<td>rinsing with octenidine for 9 days</td>
<td>after 9 days the microbiologic cultures became negative</td>
<td>during the next 30 months there was no recurrence of the inflammation process</td>
</tr>
<tr>
<td>BM</td>
<td>74</td>
<td>M</td>
<td>57</td>
<td>chronic inflammation of the distal part of the tight bone resulting from a gunshot wound in 1944</td>
<td><em>A. baumanii</em>, <em>P. aerugi-no-sa</em>, <em>CNS</em>, <em>Corynebacterium</em> spp.</td>
<td>29 days of irrigation-drainage with octenidine while continuing local antibiotherapy</td>
<td>on the 10th day of octenidine use the microbiologic cultures became negative and remained so through the end of the treatment</td>
<td>As of 2010 there has been no recurrence of the inflammation process</td>
</tr>
<tr>
<td>Initials (Inicjały)</td>
<td>Age (Wiek)</td>
<td>Sex (Płeć)</td>
<td>Hospital stay in days (Czas pobytu w szpitalu – dni)</td>
<td>Diagnosis (Rozpoznanie)</td>
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<tr>
<td>KP</td>
<td>68</td>
<td>F</td>
<td>110</td>
<td>septic inflammation of hip joint after alloplasty</td>
<td>Salmonella spp., S. haemolyticus, CNS, E. coli, S. maltophilia, Pseudomonas spp., Candida spp., E. faecalis</td>
<td>on the 12th day of hospitalization, after wound debridement, the wound was rinsed with octenidine solution (2 minutes); subsequently octenidine/water irrigation-drainage was applied daily</td>
<td>on the 24th day of octenidine use the microbiologic cultures became negative and remained so through the end of the treatment</td>
<td>The patient was released to her home with her hip inflammation healed. As of 2010 there has been no recurrence of the inflammation process</td>
</tr>
<tr>
<td>RR</td>
<td>53</td>
<td>F</td>
<td>21</td>
<td>hip alloplasty following joint repositioning (12 cm distraction) to treat congenital dislocation</td>
<td>E. faecium, CNS</td>
<td>wound debridement; irrigation-drainage with octenidine solution</td>
<td>after 8 days of treatment with Octenisept® the microorganisms were eradicated</td>
<td>during the next 36 months there was no recurrence of the inflammation process</td>
</tr>
<tr>
<td>SM</td>
<td>56</td>
<td>F</td>
<td>23</td>
<td>septic alleged shin joint</td>
<td>S. aureus, CNS</td>
<td>starting on the 9th day, treatment with swabs soaked with octenidine was applied for two minutes per day, followed by rinsing and swabs soaked with water for injections. In addition to antisepsis, intravenous antibiotherapy was used in accordance with an antibiogram</td>
<td>on the 5th day of octenidine treatment, the microbiologic cultures became negative and granulation occurred in the area of skin loss and the implantation site; granulation was stimulated by the application of swabs soaked with hypertonic salt solutions</td>
<td>during the next 30 months there was no recurrence of the inflammation process</td>
</tr>
</tbody>
</table>
were eradicated in all patients involved in the experiment. During 30 months of observation, none of the patients experienced a recurrence of the inflammatory process.

Discussion

The treatment of osteoarticular infections entails enormous costs: the patient's hospitalization in the orthopedic ward, the use of expensive antbiotherapy and the necessity of multistage operative treatment.

In recent years, the use of antibiotic irrigation-drainage has become increasingly controversial due to the possibility of chemical damage to the tissue and interference with wound healing.

At the Specialist Hospital in Kosciierzyna, in cases of acute osteitis the authors currently employ multistage procedures: the evacuation of necrotic tissue, followed by irrigation-drainage with Ringer’s solution (0.5–1 L/hour), with simultaneous general antbiotherapy. The antibiotic therapy is empiric at first, and then for a period of seven days it is administered in accordance with the results of the microbiologic cultures performed. Afterwards it is administered orally for a three-week period [3].

Encouraging results from the use of octenidine dihydrochloride in the treatment of chronic wound infections, as well as its good tissue tolerability and low cytotoxicity, prompted the authors to investigate its efficacy in the treatment of chronic osteitis.

Intraoperatively, the wound was rinsed with Octenisept® during the debridement of the inflammatory focus; and after surgery, irrigation-drainage with Octenisept was used. Analytical procedures showed no changes in blood morphology after the use of Octenisept, and neither systemic nor local complications occurred during its use. The microbiologic procedures performed showed high antiseptic efficacy resulting in the eradication of the pathogenic microorganisms.

References


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Conflict of interest: None declared

Received: 2.07.2010
Revised: 13.09.2010
Accepted: 4.10.2010