

CORR Insights®: Is NS-EDTA Effective in Clearing Bacteria From Infected Wounds in a Rat Model?

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Where Are We Now?

Research on wound irrigation additives such as antiseptics, antibiotics, or soaps holds promise to prevent infections after surgery, improve wound and open fracture healing, and reduce the likelihood of reoperation [1-3, 8, 9]. While many existing additives show improved bacterial clearance in vitro, the benefits of these additives have often

failed to appear in vivo, and in some cases cause harm [1, 2, 7, 8]. Bacitracin and castile soap have been associated with rebound bacterial growth, delayed wound healing, and increased reoperation [1, 7, 8]. High-pressure pulse lavage more effectively clears bacteria from metal and bone in vitro, but is no better than gravity flow or bulb syringe in human extremity wounds [2, 7, 8]. Current evidence suggests that low-pressure normal saline is the most effective existing fluid, because of its low cost and absence of deleterious impacts on host tissues [1, 7, 8].

The authors of the current study [11] were interested in an alternative to antiseptics, antibiotics, and soaps, and specifically studied normal saline-EDTA because of its potential to improve bacterial clearance by chelation of cations necessary for bacterial adhesion, without causing injury to local host cells. They performed a study in a rat model and human cell cultures and found that normal saline-EDTA is more effective than normal saline or castile soap for clearing *Staphylococcus aureus* or *Escherichia coli*, and results in a reduced number of débridements to obtain culture-free wounds. No direct toxicity was observed to human fibroblasts or endothelial cells. Based on this

study, it seems that normal saline-EDTA is a promising candidate as a wound irrigation solution, as it is inexpensive, nontoxic, and effective in the clearance of typical bacteria.

Where Do We Need To Go?

Although investigating rat models and specific bacterial cultures (*S aureus* and *E coli*) helps us determine the potential of normal saline-EDTA, these types of studies may not fully represent the reality of large-animal and human wounds with polymicrobial contamination, and many questions remain: What is the effect of normal saline-EDTA on other species of bacteria? What effect might soil or other contaminants have on the ability of EDTA to chelate ions involved in bacterial adhesion? Are there any potential risks of normal saline-EDTA over large surface area wounds? What concentration of EDTA is most effective?

Even though EDTA appears nontoxic, rapid administration of intravenous EDTA can result in acute hypocalcemia. In rats, intramuscular injection of EDTA can result in hypocalcemia, and intraperitoneal administration of normal saline-EDTA can influence the hypothalamic-pituitary axis [4]. In humans, death has been reported resulting from the use of intravenous-EDTA, either from unintentional use, or from too rapid

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administration during chelation therapy [10]. In 2008, intravenous disodium-EDTA was withdrawn from the U.S. market, and the FDA withdrew its approval [10]. Although calcium-EDTA is helpful for chelation and removal of heavy metal poisoning, hospitals have been advised to avoid stocking it due to the potential confusion between calcium-EDTA and sodium-EDTA for infusion [10]. Could intraperitoneal administration of normal saline-EDTA for open pelvic fractures, or repeated irrigation of large areas of muscle result in hypocalcemia, or other unanticipated systemic side effects [1, 4, 8, 10]?

Overall, we need a better understanding of the regional and systemic effects of EDTA as a chelation agent in order to properly determine its mechanism of action, and to evaluate in more detail its safety as an irrigation additive for use in wounds. It is important to settle these controversies, because if there is one thing that can be taken from existing literature on irrigation additives, it is that they can have unintended consequences [1, 7, 8].

How Do We Get There?

Researchers should perform additional animal studies in order to establish a safety plan before performing large comparative studies in humans. Further rat studies with other bacterial species and polymicrobial contamination would help determine the ability of EDTA to disrupt adhesion in different kinds of bacterial infections. Studies with established large-animal wound models may help us better understand

the influence of EDTA irrigation in animals similar to humans [7]. Genetically altered luminescent bacteria allow for the quantification of bacteria without tissue sampling in large open wounds using photon-counting cameras, and the evaluation for bacterial regrowth after irrigation [7]. This is important for effectiveness, but also for the ideal timing of sequential débridement irrigation [7].

The safety of normal saline-EDTA for use in large wounds will also need to be evaluated using animals prior to human studies. Normal saline-EDTA has already been used routinely in dental practice (endodontics) and veterinary practice (irrigation of ears of dogs), [5, 6] but it has not been used in studies with high-volume irrigation and large-body surface area. Large animal studies with intraperitoneal and/or extensive intramuscular irrigation of EDTA could be combined with venous sampling to help determine the serum levels of calcium, magnesium, and zinc following irrigation. Local tissue samples may also be assessed for their histological appearance and local calcium concentrations.

Research that compares irrigation fluids in a study like the multicenter, blinded Fluid Lavage of Open Wounds investigation [8], which examined the impact of irrigation fluids, could show a difference in infection or rate of reoperation. This type of study should determine which concentration of EDTA is most appropriate, and whether there are any potential risks of application of EDTA over large wounds. The cost of preparation, storage, and safe administration of normal saline-EDTA will also need to be balanced against the effectiveness of the

additive to determine whether it is appropriate for broad clinical use.

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