

Scolicidal Agents and Secondary Cholangitis

Dr. Sudheer Tale^{1*}, Dr. Srinivas Bannoth^{2*}, Dr. Pahel Soibam Meitei^{3**},
Dr. Mohan Kumar Hanumanthappa^{1*}, Dr. Mrudula Kolli^{1#}

¹Senior Resident, Department of Internal Medicine, ²Senior Resident, Department of General Surgery,

³Assistant Professor, Department of Internal Medicine

*Post Graduate Institute of Medical Education and Research, Chandigarh - 160012.

**JNIMS, Imphal.

#Gandhi Medical College, Hyderabad.

Corresponding Author: Dr. Srinivas Bannoth

ABSTRACT

Aim: The aim of this study was to review different scolicidal agents in present use, side effects and newer scolicidal agents which could effectively had lethal effect on echinococcus in various in-vitro and in-vivo studies.

Methods: Various in vitro and in vivo animal and human studies had been reviewed in this study, effects of various scolicidal agents and their side effects have been presented.

Conclusion: Hypertonic saline the most commonly used scolicidal agent has potent action but is not devoid of its complications even 5% percent hypertonic saline could cause sclerosing cholangitis in rabbit model, so 20% saline which is more commonly used scolicidal could have more sclerosing effects on biliary tree in case of intra cystic communication and is also associated with hypernatremia. 10% povidone iodine had similar scolicidal effect like hypertonic saline, and its intra cystic use has shown upto 50% sclerosing cholangitis in some studies. Cetrimide a potent scolicidal agent has been associated with sclerosing cholangitis and has been reported to cause severe intra operative metabolic acidosis. Silver nitrate too showed histopathological changes in liver and biliary tract and was associated with methemoglobinemia. The new scolicidal agents being studied were hypertonic glucose solutions, 10% honey, methanolic extract of sambucus ebulus, chloroformic extract of garlic, ethanolic extracts of turmeric and ginger and black cumin seed oil have shown to be potent scolicidal agents and some of them showed that they were devoid of sclerosing cholangitis, so a further large scale and human studies are essential to reproduce these results and to evaluate their side effects. Recently used nano particles of selenium though showed scolicidal effects were associated with complications. So presently used scolicidal though they are potent in action are associated with sclerosing cholangitis, hence a careful intracystic use of them in case of intracystic biliary communication is essential. They were associated with severe cholangitis, and routine practice of use of scolicidal agent in spite of biliary cystic communication should be avoided. The newer agents which could be safe in these aspects need further large scale studies.

Key words: Scolicidal agents, Sclerosing cholangitis, Echinococcus

INTRODUCTION

Cystic echinococcosis (Hydatid cyst, CE) is a parasitic infection caused by the larval stage of dog tapeworm echinococcus granulosus. It has been identified as a major public health and economic problem in

developing countries including Iran. ⁽¹⁾ The most common form of treatment is open surgical removal of the cysts combined with chemotherapy using albendazole and/or mebendazole before and after surgery. ⁽²⁾

At present, surgery remains the preferred treatment for particular WHO stage disease. In addition, chemotherapy with benzimidazoles and PAIR (puncture, aspiration, injection, and reaspiration) are recommended as alternative treatments to surgery, especially for the patients who cannot tolerate surgery. (3,4)

Various chemical scolicidal agents such as hypertonic saline, Ag-nitrate, cetrimide, and ethanol have been used for inactivation of protoscolices during surgery, but most of them are associated with adverse side effects such as sclerosing cholangitis (biliary tract fibrosis), liver necrosis, and methemoglobinemia. (5,6)

Thus, a rapid and complete scolicidal effect with no local or systemic side effects and also low cost are some properties of an ideal scolicidal solution for hydatid cyst surgery. (7)

Different scolicidal agents such as hypertonic saline, silver-nitrate, cetrimide, and ethanol, povidone-iodine have been used for inactivation of protoscolices during surgery, but most of them are associated with adverse side effects such as hypernatremia, sclerosing cholangitis, metabolic acidosis, liver necrosis and methemoglobinemia. Thus, the development of new scolicidal agents with high efficacy in a shorter time of exposure, scolicidal ability inside a cyst, lower toxicity, higher availability and ability to be prepared rapidly is an urgent need for surgeons. (5-7)

MATERIALS AND METHODOLOGY

In this article we have reviewed various in vitro and in vivo human and animal studies about present day scolicidal agents which are most commonly used and newer agents which had shown promising results in respective studies. Most of studies have used rat models to know efficacy of scolicidal agents and their rare but some of concerning side effects.

Statistical analysis:

Studies under review have used different analysis test like Mann Whitney U test, student t test, paired sample t-test, logistic regression analysis, Kruskal Wallis single-

direction analysis using SPSS soft ware package.

DISCUSSION

The aim of this study was to review different scolicidal agents in present use, side effects and newer scolicidal agents which could effectively had lethal effect on echinococcus in various in-vitro and in-vivo studies. Present day commonly used scolicidal agents are 20% saline, 3% hydrogen peroxide, 1.5% cetrimide-0.15% chlorhexidine (10% Savlon), 95% ethyl alcohol, 10% polyvinylpyrrolidone-iodine (Betadine).

Hypertonic saline has been used in various concentrations as scolicidal agents with range of 3-30%, however hypertonic saline of 20% had strong scolicidal effect which could kill all protoscolices at the end of 9 minutes. Hypertonic saline of 10% killed ninety percent of scolices at the end of thirty minutes. (8) Studies of Khosrov had showed that saline concentrations of 1%, 3%, 5% were ineffective even at the end of 30 minutes. (8) Similar results were demonstrated by Kayaalp in which 5% saline was ineffective even at 60 minutes and 10% saline was ineffective upto 75 minutes. (9)

Though worldwide being most commonly used scolicidal agent, it is not devoid of its complications, most of studies have demonstrated sclerosing cholangitis after intracystic use of hypertonic saline. Studies of S V Hosseni had showed that even 5 % percent hypertonic saline could cause sclerosing cholangitis in 30 % rabbit model, so 20 % saline which is more commonly used scolicidal could have more sclerosing effects on biliary tree in case of intra cystic communication. (5)

Studies of M, Balkan A showed significant elevations in liver function tests, significant increase in alkaline phosphatase, there was increased production of free radicals and rise in levels of malonyldialdehyde which was suggestive of increased free radicals. In addition his to pathological changes of portal

inflammation, fibroblastic reaction, parenchymal necrosis and sclerosing cholangitis was seen. ⁽¹⁰⁾ In addition to this study done by Ali Nayyef Asi had shown increased levels of SGOT and SGPT IN 27.5 % of patients and increase in bilirubin upto 7.5% of patients. Recurrence rate of upto 30 percent in spite of use of 20 % hypertonic saline as scolicidal agents after follow up of 5 years. ⁽¹¹⁾

Another potential complication of hypertonic saline being hypernatremia. Krige et al found fatal hypernatremia in their patient which resulted in death of one of their patients. ⁽¹⁵⁾

Povidone iodine is a stable complex of polyvinylpyrrolidone and elemental iodine, 10 % povidone iodine is most commonly used scolicidal agent. Ali Nayyef had showed increased levels of SGOT and SGPT in around 20 % of patients and increase in serum bilirubin levels upto 5 % of patients with recurrence rate of 12.5 percent on follow up, ⁽¹¹⁾ similar recurrence rate of around 11 % was shown by Handy. ⁽¹⁷⁾

Studies by Sungur on povidone iodine though showed its adequate scolicidal effect, but had sclerosing cholangitis in 50 percent of animals used in the study. ⁽¹²⁾ In an experimental study with 10% povidone iodine by Coskun et al reported marked stasis in liver, piecemeal necrosis, periportal inflammation. In another study renal shut down, sterile peritonitis, sclerosing serositis and constrictive pericarditis has been described. ⁽¹³⁾ Eyupoglu et al found significant histopathological changes in liver and marked alterations of liver enzymes even in low concentrations of povidone iodine. ⁽¹⁴⁾

Cetrimide and chlorhexidine are cationic detergents and are more effective in alkaline medium. Hydatid solutions are alkaline for this reason these agents may be considered as scolicidal agents. Cetrimide 0.5% can exert scolicidal effect in 10 minutes in an experimental media. Although combination of 5% cetrimide and 0.05% chlorhexidine provides high grade

neutralization in hydatid solutions some studies reported live protoscolices in some cases. Studies of Seyed Hosseni showed cetrimide had potency of 100% scolicidal after 1 minute of exposure. ⁽⁵⁾

Biochemical alterations in liver function test have been observed after use of cetrimide and increase in free radical productions has been seen. Histopathological changes of centrilobular cholestasis, piecemeal necrosis, peripheral parenchymal necrosis and changes of sclerosing cholangitis have been observed. Case reports of cetrimide induced metabolic acidosis have been reported. ⁽⁵⁾ Though complication was rare, has lead to severe intraoperative metabolic acidosis. So during use of cetrimide as scolicidal agent a caution is to be observed to use in low concentrations and intraoperative monitoring of acid base gas analysis. ⁽¹⁶⁾

Silver nitrate as scolicidal agent is one of common surgical practice. Studies of S V Hosseni have showed histopathological changes after use of 0.5 % silver nitrate and around 73 % of rabbits have shown sclerosing cholangitis. Studies of Sahin have shown significant intensity of histopathological changes after use of silver nitrate. Fatal reactions and severe methemoglobinemia have been reported. ⁽⁵⁾ Eyupoglu et al observed portal inflammation, necrotizing areas in parenchyma, Kupffer cell hyperplasia after use of silver nitrate. ⁽¹⁴⁾

Hydrogen peroxide which decomposes into water and oxygen part from use as antiseptic has also been used as scolicidal agent. Studies of Hamdy which compared 3 % hydrogen peroxide and povidone iodine have shown that peroxide was more effective than 10 % povidone iodine. They reported 0 % recurrence rate after use of hydrogen peroxide when compared to povidone iodine which had recurrence in 11 % of patients. ⁽¹⁷⁾ Omzen et al used 10 % hydrogen peroxide as scolicidal agent and found that no patient had recurrence. ⁽¹⁸⁾

Hypertonic glucose has been reported as effective protoscolicidal agent. S V Hosseini studied protoscolicidal effects of hypertonic saline with concentrations ranging from 10% to 50%. No significant scolicidal action was seen upto 25% but 50% hypertonic glucose was after 5 minutes of exposure had 97.3% scolicidal effect but complications associated with hypertonic glucose were not studied. (19) Studies of Mojtaba Shahnazi had similar findings both 40% and 50% glucose were 100 percent scolicidal after exposure to 20 minutes. Hosseini et al experiments showed that no changes in biliary epithelium and liver parenchyma were seen after injection of hypertonic glucose in rabbit gall bladder ranging from 25 to 50%. (19)

Honey concentrations of 10% or greater killed all protoscolices. No systemic side effects, such as anaphylactic reaction or hyperglycemia, and no local side effects in peritoneal surface developed with intraperitoneal administration. Studies of Bulent Kilicoglu in Wistar albino rats after injection of 10 percent honey in biliary tree

At the end of the sixth month, liver function tests were found to be normal. The tissue samples of liver and ductus choledochus of the honey group showed no histomorphologic difference from the control group. No stricture on the biliary tree was detected on the retrograde cholangiograms. (20)

Methanolic extract of sambucus ebulus fruit showed high scolicidal activity. In vitro studies S H Gholami showed methanolic extracts of S. ebulus of 1, 10, 50 and 100 mg/ml were highly scolicidal at 5, 10, 30 and 60 min of application, respectively. (21)

Chloroformic garlic extract at concentration of 20% is found to be statistically effective scolicidal agents in in-vitro models comparable to other commonly used scolicidal agents. Cholangiographic results in rabbits showed that eight percent of rabbits shown changes of sclerosing cholangitis after use of chloroformic garlic extract. (22)

Selenium is the main component of selenoenzymes, which are found to protect animal cells from oxidative damage. Studies of Hosseini have shown Selenium Nanoparticles have a potent scolicidal activity especially at concentrations 500 and 250 mg/ml (100% mortality rate) after 10 and 20 min of application, respectively. Thus, these results revealed that scolicidal effects of Selenium nanoparticles at concentration 500 mg/ml were comparable with scolicidal effects of 20% hypertonic saline (15 min). (23)

Studies of Esam Almalki showed ethanolic extracts of turmeric and ginger as potent scolicidal agents. Three concentrations of each (10, 30, 50 mg/ml) were investigated and viability of scolices was tested by 0.1% eosin. Ginger extract showed strongest scolicidal effect (100%) after 20 min at concentration of 30 mg/ml and 10 minutes at 50 mg/ml while maximum scolicidal effects of turmeric was 93.2% after 30 minutes at a concentration of 50 mg/ml. (24)

In vitro studies of Hosseini on scolicidal effects of black cumin seed oil showed that at concentration of 10 mg/ml and its main component thymoquinone at 1 mg/ml had potent scolicidal effects against scolices after exposure to about 10 minutes. (25)

CONCLUSION

Hypertonic saline the most commonly used scolicidal agent has potent action but is not devoid of its complications even 5% percent hypertonic saline could cause sclerosing cholangitis in rabbit model, so 20% saline which is more commonly used scolicidal could have more sclerosing effects on biliary tree in case of intra cystic communication and was associated with hypernatremia. 10% povidone iodine had similar scolicidal effect like hypertonic saline, and its intra cystic use has shown upto 50% sclerosing cholangitis in some studies. Cetrimide a potent scolicidal agent has been associated with sclerosing cholangitis and has been reported to cause

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