ORIGINAL PAPERS

Adv Clin Exp Med 2014, **23**, 3, 395–398
ISSN 1899–5276

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Is Cetrimide-Chlorhexidine Risky for Secondary Sclerosing Cholangitis?

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. The liver is the most frequent organ for placement of hydatid cyst disease. All known protoscolicidals that are used for *echinococcus* degeneration have a risk of caustic secondary sclerosing cholangitis. The cetrimide-chlorhexidine combination is an effective protoscolicidal agent for treatment of hydatid liver cysts.
Objectives. The aim of this experimental study was to examine this combination for potential risks of caustic secondary sclerosing cholangitis.
Material and Methods. Thirty rats were enrolled and divided into two groups. In the study group, 0.15 mL of a cetrimide (0.5%) and chlorhexidine (0.05%) combination was injected into the bile ducts for five minutes. The control group included the same amount of normal saline and waiting period. The rats were followed for 120 days and the living rats were examined for biliary injury by biochemical analysis and histopathology.
Results. No specific histopathological findings for caustic sclerosing cholangitis such as bile duct stricture or periductal fibrosis were present in any groups. Other pathological criteria demonstrating inflammation including portal inflammation, bile duct proliferation and necrosis were similar in both groups. Biochemical analysis including a liver function test (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyltranspeptidase) appeared similar to the control group.
Conclusions. A cetrimide 0.5% and chlorhexidine 0.05% combination has similar liver function results and histopathological effects to normal saline on bile ducts and it appears to be safe for bile ducts (**Adv Clin Exp Med 2014, 23, 3, 395–398**).

Key words: cetrimide, chlorhexidine, bile duct, cholangitis, echinococcus granulosus.

Hydatid disease has a worldwide distribution and the most frequently effected organ is the liver. Treatment of hydatid liver cysts has included removal of cyst contents and inactivation of protoscolices via surgery or interventional radiology. Several agents such as formalin, hypertonic saline, ethanol, hydrogen peroxide, silver nitrate, chlorhexidine or cetrimide are used for inactivation of the protoscolexes [1]. Rupture of the liver cysts into the bile ducts is the most frequent complication, with an incidence of 21% to 37% [2, 3]. Therefore, agents should be effective against protoscolexes and should be non-toxic to the biliary tract. However, most of known protoscolices (formalin, hypertonic saline, ethanol, hydrogen peroxide and silver nitrate) carry the risk of chemical secondary sclerosing cholangitis [4]. Despite the widespread clinical use of cetrimide and chlorhexidine, there is no reported case of sclerosing cholangitis except in one experimental study [5]. Here, we aimed to compare the effects on the biliary tract of a cetrimide-chlorhexidine combination to normal saline in a new experimental study.

Material and Methods

This study was done in the Gulhane Military Medical Academy Researchi Laboratory with the permission of the Ankara University Ethics

Committee. Thirty female Sprague-Dawley rats weighing 90 g to 120 g were used. We preferred sevoflurane inhalation anesthesia to minimize the hepatoxic effects of other anesthesia drugs. After a midline abdominal incision, we punctured the duodenum with a 24G intravenous indwelling cannula (Introcan-W, Braun, Melsungen, Germany). The inner needle was withdrawn and the outer silicon catheter was slightly pushed along the mesenteric border of the duodenum. The tip of the catheter was introduced through the ampulla and then into the bile duct without difficulty. The tip of the catheter was placed near the liver hilum to avoid any injection into the pancreatic duct. In the study group, 0.15 mL of a cetrimide (0.5%) and chlorhexidine (0.05%) combination (Savlex, Drogsan' Ankara, Turkey) was injected and in the control group, the same amount of normal saline was injected into the bile ducts. Injections were done randomly and without any pressure. We did not remove the catheter from the bile duct for 5 min to establish enough time for drug contact. At the end of 5 min, we removed the catheter and closed the abdomen. There were 2 operative mortalities in each group and the remaining 28 rats were followed for 120 days. At the end of the follow-up period, the living rats were examined for histopathological and biochemical analysis. Laparotomy and thoracotomy were performed under inhalation anesthesia. Specimens of the median lobes of the liver and extrahepatic bile ducts near the hepatic hilum were taken and fixed with solution immediately. Histopathological examinations were done after hematoxiline-eosine dying. A pathologist examined the specimens blindly for 5 criteria which were (I) portal inflammation, (II) bile duct proliferation, (III) necrosis, (IV) bile duct stricture, and (V) periductal fibrosis. Blood samples were taken directly from the heart and 4 liver function tests (aspartate and alanine aminotransferase, alkaline phosphatase and gamma-glutamyltranspeptidase) were examined in both groups.

The statistical analyses were performed with SPSS for Windows version 13.0 (SPSS Inc., Chicago, IL, USA). Continuous variables (the biochemical results) were compared as independent samples using a Student's *t*-test. Categorical variables (the pathological results) were compared using either the Pearson chi-square test or Fisher's exact chi-square test as appropriate. Values of $p < 0.05$ were considered to be statistically significant.

Results

At the end of 120 days, 18 rats were alive, 9 in both groups. The mortality reasons of the rats were not available; however, there was no difference in the number of live rats in both groups. Macroscopically, there were no necrotic areas on the liver or biliary ducts that have been reported before in some studies [5]. The histopathological results are summarized in Table 1. Intra- and extrahepatic portal inflammation was the most frequent (44––67%) pathological finding in both groups. There was no difference among the groups for portal inflammation. Intra- and extrahepatic bile duct proliferation was only present in 1 rat in the cetrimide-chlorhexidine group. Necrosis was the second most frequent finding and there was no difference between the groups. More specific pathological findings for caustic sclerosing cholangitis such as bile duct stricture and periductal fibrosis were not present in any groups. Biochemical analysis showed similar and even improved results in the cetrimide-chlorhexidine group than in the normal saline group and are summarized in Table 2.

Discussion

An ideal protoscolicidal agent should be effective against the parasite with low adverse effects to the host. One of the most undesirable side effects

Table 1. Histopathological results of both groups

Parameters	Intrahepatic bile ducts			Extrahepatic bile ducts		
	ns. (n = 9)	cc (n = 9)	p	ns. (n = 9)	cc (n = 9)	p
Portal inflammation	4	5	1.00	5	6	1.00
Bile duct proliferation	0	1	1.00	0	1	1.00
Necrosis	5	3	0.63	2	4	0.62
Bile duct stricture	0	0	1.00	0	0	1.00
Periductal fibrosis	0	0	1.00	0	0	1.00

ns. – normal saline (0.9%).
cc – cetrimide (0.5%) and chlorhexidine (0.05%).

Table 2. Biochemical results

Parameters	ns. (n = 9)	cc (n = 9)	p
Aspartate aminotransferase (U/L)	165 ± 52	124 ± 19	0.04
Alanine aminotransferase (U/L)	68 ± 28	54 ± 12	0.18
Alkaline phosphatase (U/L)	248 ± 65	181 ± 71	0.05
Gamma-glutamyltranspeptidase (U/L)	7 ± 7	4 ± 4	0.28

ns. – normal saline (0.9%).
cc – cetrimide (0.5%) and chlorhexidine (0.05%).

is caustic sclerosing cholangitis. It has been demonstrated in experimental or clinical studies that most agents used in clinical practice carried a risk of caustic sclerosing cholangitis [4]. Factors for caustic sclerosing cholangitis after hydatid cyst surgery were (i) the existence of cysto-biliary communication, (ii) protoscolicidal injection into the cyst cavity, (iii) a sufficient time period for contact to the biliary duct, and (iv) the power of the toxic effect of the agent [4].

Several pathological findings such as portal inflammation, bile duct proliferation, necrosis, bile duct stricture, and periductal fibrosis occur after protoscolicidal contact [6]. It was reported that some parameters such as inflammation, proliferation or necrosis are non-specific, but bile duct stricture and periductal fibrosis are typical for caustic sclerosing cholangitis [5]. Houry and associates [7] reported that a 2% formaldehyde injection resulted in periductal fibrosis and bile duct strictures. Zilan and co-workers [8] administered 3% H_2O_2 and 10% H_2O_2 into the bile ducts and all these agents were found to cause periductal fibrosis. Tozar and associates [8] had a similar experimental study about the cetrimide-chlorhexidine combination and they found periductal fibrosis in 11 of 20 rats. Contrary to their results, we did not find any histopathological fibrosis or stricture of the bile ducts after cetrimide-chlorhexidine injection. It is difficult to explain the difference of the results of this previous study and our results. Despite similar experimental modeling, we used sevoflurane, a minimal hepatotoxic inhalation anesthetic, we waited for 120 days instead 90 days to terminate the study and lastly we examined intrahepatic bile ducts as well as extrahepatic.

The cetrimide-chlorhexidine combination as a protoscolicidal has been used widely in most surgical clinics. The combination of cetrimide and chlorhexidine was found to be a very potent protoscolocidal agent in previous clinical and in vitro studies [9, 10]. We have used it for almost 15 years in more than 200 hydatid cyst cases without any complications. As far as we know, there have been no reported cases of caustic sclerosing cholangitis after cetrimide-chlorhexidine use. Some points of this study lead us to make a clear statement; (i) no difference of mortality rates during the study period between the groups, (ii) not worse liver function tests or histopathological findings in the cetrimide-chlorhexidine group (iii) absence of any of the specific histopathological results such as fibrosis or stricture of the bile ducts after cetrimide-chlorhexidine injection. These results lead us to believe that a cetrimide-chlorhexidine combination may be a safer protoscolicidal agent for caustic sclerosing cholangitis.

Previously, most of the well known protoscolicidals were reported as risky for the bile ducts. Authors report that a cetrimide 0.5% – chlorhexidine 0.05% combination has the potential of to be safer for bile ducts.

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Conflict of interest: None declared

Received: 2.10.2012
Revised: 25.02.2013
Accepted: 9.06.2014