Original paper

Povidone Iodine and Hypertonic Saline Induced Sclerosing Cholangitis in Hepatic Hydatid Cysts Surgery

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Abstract

Background: Surgery is the treatment of choice for hepatic hydatid disease but surgical treatment carry the risk of recurrence if we do not use a proper scolicidal agent and may convert patient with solitary hepatic hydatid cyst to patient with many incurable cysts. The ideal scolicidal agent should kill vital scolices, and not have local or systemic adverse effect, and not toxic to bile duct. Yet, there is no ideal scolicidal agent involving such effects. One of the important serious complications after instillation of scolicidal agents is sclerosing cholangitis.

Aim: to assess the risk and severity of povidone iodine and hypertonic saline induced sclerosing cholangitis in guinea pigs.

Materials and methods: In this study we used twenty guinea pigs which were divided into two equal groups. In the first group 0.3 ml10% povidone iodine was injected to the biliary tree after clamping then released after five minutes and second group, 0.3 ml 20% hypertonic saline was used.

Four months later on the pig was euthanized by ether and three biopsies taken from the liver and sent for histopathological examination. Afterwards, the liver, gall bladder, the common bile duct and the duodenum were excised in one piece and immediately transferred for cholangiography. Two X-ray films were taken for each specimen in lateral and antero-posterior view after contrast material injection.

Results: in povidone iodine group 8 animals (80%) had sclerosing cholangitis while in hypertonic saline group only 2 animals (20%) had sclerosing cholangitis. This difference between the two groups was statistically significant.

Conclusions: Usage of 10% povidone iodine as a protoscolicidal agent carry high risk of sclerosing cholangitis.

Keywords: Povidone iodine, hypertonic saline, sclerosing cholangitis, Guinea pig.

Introduction

Hydatid disease is an old endemic condition in many countries all over the world caused by tapeworm echinococcus which affect sheep, cattle, pig and human. This parasite is usually observed as larva in the intestines of dogs or some carnivorous animals eating meat contaminated with hydatid cyst. Thousands of eggs are spread out with the animal feces. These eggs resistant to environmental conditions hatch into embryos in the stomach and duodenum of human or herbivorous animals that ate contaminated food with animal feces. Then, they transform into invasive active form. Passing through the jejunum mucosa, embryos reach liver with portal circulation and then hook to sinusoid. Occasionally embryos pass the first filtration and settle in lungs or bone, brain and other organs [(1)].

The hydatid disease is commonly called dog tapeworm disease and the incidence of this disease is high in countries with sheep breeding e.g. Australia, Greece, Newzeland, South America, Turkey, Iran and Iraq [(2,3)].

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About 75% of all hydatid cysts in humans are found in the liver & 15% in the lungs (the second filter). The outmost layer of a cyst, the ectocyst or pericyst, is formed by compressed and fibrotic host tissue and may become calcified, whereas inner layers are of parasitic origin and act as a germinal center. A cyst may or may not contain daughter cysts [4].

Although there are recent advances in the diagnosis and treatment of hydatid disease but it is still an important cause of significant mortality and morbidity.

Surgery is the treatment of choice for hydatid cyst of the liver since the result of medical and percutaneous treatment are still controversial. In the surgical management of this disease, neutralization of the parasite, evacuation of the cyst and the management of the residual cavity are the principal step. Prevention of spillage into the peritoneal cavity and wound edges is very important. Injecting a scolicidal agent into the unopened cyst and walling off the operative field with sponges soaked in scolicidal agent are the two most commonly employed measures [5,6].

Surgical treatment carry the risk of recurrence if we do not use a proper scolicidal agent and may convert a patient with solitary hepatic hydatid cyst to a patient with many incurable cysts due to contents leakage during aspiration or evacuation of cyst[7].

Different scolicidal agents, e.g. silver nitrate, savlon, formaldehyde, chlorhexidine, hypertonic saline, povidone iodine (betadine), ethyl alcohol, hydrogen peroxide, mebendazole and albendazole were used all over the world but most of them have been abandoned due to early or late complications[8].

Scolicidal effects of these agents as well as the risk of complications are concentration dependent [6]

One of the important serious complications after instillation of scolicidal agents is sclerosing cholangitis, probably due to scolicidal agents instilled [9].

Many investigations on the incidence of this complication following administration of different scolicidal agents were performed [10].

The ideal scolicidal agent for hydatid cyst should kill vital scolices, have no local or systemic adverse effects, and not toxic to bile duct. Yet, there is no ideal scolicidal agent involving such effects. Nevertheless today there are many agents in use for the treatment of hydatid cyst [11].

In Shiraz (Iran) evacuation of the cyst after instillation of hypertonic saline is the most common surgical procedure in the treatment of hepatic hydatid cyst while in Kerbala (Iraq) the instillation of povidone iodine is a common procedure.

In this present study, we compared the incidence and severity of sclerosing cholangitis after injection of 10% povidone iodine or 20% hypertonic saline into the gall bladder of the guinea pigs.

To evaluate the safety of 10% povidone iodine versus 20% hypertonic saline as scolicidal agents.

Materials and methods

This study was carried out at the Laboratory Animal Research Center of Shiraz University of Medical Sciences for a period of about six months from October 2015 to April 2016.

In our study we used twenty healthy male/ female guinea pigs weighting 250-350g and randomly divided by block randomization method into two equal groups. Each animal was anaesthetized by intramuscular injection of Ketamine chlorhydrate (44 mg/kg) and Xylazine (8mg/kg).

After that shaving of the abdomen and sterilization by antiseptic solution then sterile toweling of the abdomen. Laparotomy done through a right subcostal incision and the liver was inspected and the gall bladder and the common bile duct were identified.

The common bile duct was clamped by fine atraumatic forceps, then 0.3 ml of 20% hypertonic saline (group A) or 10%

povidone iodine (group B) were injected into the gall bladder using 25 gauged needle. After 5 minutes the clamp was released and the abdomen was checked for any bleeding or bile leakage then the incision was closed in two layers by three zero polydioxanone absorbable suture. Tetracycline ointment and streptomycin used on the incision as a local measure to prevent infection for 7 days.

The animal left in the laboratory with ideal care, feeding and observation by specialized personnel and veterinary doctor.

During that time two animals were expired one after three days and another after one week both of them were excluded and replaced by another two and operated in the same way.

After 4 months the animals were euthanized using ether solution, then histological examination and cholangiography were performed.

Three liver biopsies were prepared from each pig and fixed in 10% formalin solution and sent for histopathological study.

Afterwards, the liver, gall bladder, the common bile duct and the duodenum were excised in one piece and immediately transferred to radiology department in a normal saline solution containing ice and cholangiography underwent. The common bile duct clamped at the level of the ampulla and one milliliter of contrast material (76% meglumin, Darupakhsh, Iran) injected to the gall bladder and then two X-ray films were taken for each specimen in lateral and antero-posterior views. All films were sent for the same expert radiologist who was blind to all samples.

The protocol of the study was approved by Ethic Committee of Shiraz University of Medical Sciences according to the principles of laboratory animal care (no.10226).

Statistics: We used Chi-square test and Man-Whitney U test to compare the results using SPSS version 16. The P-value < 0.05 was considered as statistically significant.

Results

Radiological findings of the cholangiography for both groups are shown in Table 1.

Cholangiogram findings classified into: mild, moderate or severe, depending on the number, extent and severity of narrowing, presence of cavitation and severity of the event.

Sclerosing cholangitis was significantly more in povidone iodine group.

The histopathological results of both groups are shown in table 2

Discussion

Although surgery is considered the treatment of choice for hydatid disease of the liver, controversies still exist regarding the preferred operative technique, management of the residual cavity and use of scolicidal agents. It has been traditional to inject scolicidal agents into the unopened hydatid cyst because of the risk of spillage into the peritoneal cavity leading to recurrent disease.

Table1. Cholangiographic findings in both groups (n=10)

Findings	Group A Hypertonic saline group	Group B Povidone iodine group
Normal	8	2
Multiple moderate intra and extrahepatic narrowing	0	1
Multiple moderate to severe intra and extrahepatic narrowing	0	1
Multiple moderate intra and extrahepatic narrowing, pruned tree	0	1
Minimal focal intrahepatic narrowing	2	1
Prunned tree (severe)	0	1
Severe intra and extrahepatic narrowing, prunned tree appearance	0	2
Severe intra and extrahepatic narrowing, prunned tree appearance+ multiple tiny cavities communicating with biliary tree	0	1

Fig.1. Cholangiogram of guinea pig in group B showing sclerosing cholangitis [severe intra and extrahepatic narrowing, prunned tree appearance & multiple tiny cavities communicating with biliary tree]

Table 2. Histopathological findings in biopsies of both groups of guinea pigs done after four months

Pathological Findings	Group A Hypertonic Saline group	Group B Povidone iodine group
Normal	9	8
Periportal fibrosis	1	2

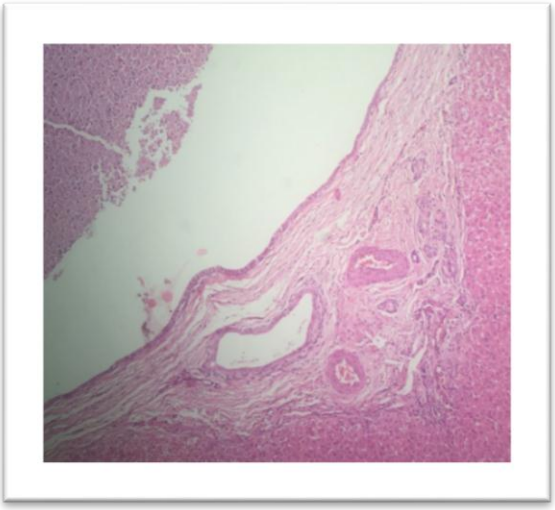

Fig.2. Histopathological findings of guinea pig in group A: Section of bile duct show mild periportal fibrosis with dilatation

Cyst fluid contains thousands of protoscolices and each one has the potential to grow into a new hydatid cyst. Among the various scolicidal agents advocated in the past, formalin was the first and most frequently used agent. Despite the effectiveness it is no longer used because of the associated toxicity [12,13].

Sclerosing cholangitis is a serious complication and mainly due to connection between the cyst and the bile ducts, this cysto-biliary fistula allow the passage of protoscolicidal agents into the biliary tract.

The pathogenesis of sclerosing cholangitis secondary to these agents is unclear. It could be due to the caustic effects by the scolicidal solution passing from the cyst into the biliary tree or immunological factors which can explain their late development and also their development in areas far from those directly exposed to scolicidal agents [14].

The connection between hydatid cysts and biliary ducts was reported between 25% and 50% [10].

There are some reports showing that the use of hypertonic saline or silver nitrate should

be avoided when their color suggests a biliary communication [15,16].

A lot of study over the world were done to find a potent scolicidal agent without risk. But all these reports indicate that sclerosing cholangitis is a major complication of surgery of liver hydatid cyst and none of their scolicidal agents were considered safe [17].

This study was done in animal model to assess the incidence and severity of sclerosing cholangitis caused by the injection of 10% povidone iodine or 20% hypertonic saline to the biliary tree.

sclerosing cholangitis is usually diagnosed by Cholangiography which considered as the standard method of diagnosis [18,19,20,21].

While the pathological findings are usually nonspecific and cannot separately be used for diagnosis of sclerosing cholangitis [18,22].

For these reasons which are compatible with our observations and results [table2, fig.2] we used cholangiographic findings as a diagnostic criteria of sclerosing cholangitis.

In both primary and secondary sclerosing cholangitis the radiological findings in cholangiography are same, showing focal strictures, irregularities, beading and fraction of small bile ducts [20].

Koti RS et al in their book " short practice of surgery " advice that scolicidal agents used in hepatic hydatid cysts surgery are hypertonic saline (15–20%), ethanol (75–95%) or 10% povidone iodine,

But this may cause sclerosing cholangitis if biliary radicles are in communication with the cyst wall [2].

Karaoglanoglu M. et al from Turkey concluded in their work that the commonest used protoscolicidal agents are hypertonic saline, alcohol and povidone iodine [23].

Landa Garcia et al found in their study that povidone iodine show a better protoscolicidal effect than normal saline, hypertonic saline, or praziquantel[24].

Assi AN from Al-Naysseria in Iraq, in his research advised that the use of the 10% povidone iodine in surgical operation for hydatid cyst as a scolicidal because it is strongly effective against the scolices, with minimum intra or post-operative insult on the liver cells, cheap and widely available [7].

But Hamdy D. Elayouty et al from Egypt in their study found that hydrogen peroxide is a more effective and safer scolicidal drug than povidone-iodine as shown by the differences in the incidence of complications and postoperative recurrence rate [25].

BakiEkci, MD from Turkey in his article said that sclerosing cholangitis associated with povidone iodine usage as scolicidal agent is about 50% [1].

In our current study we found that incidence of sclerosing cholangitis was significantly high in the povidone iodine group (80%) in comparison with hypertonic saline group (20%).

Because of the high incidence of sclerosing cholangitis in povidone iodine group, which was significantly higher than hypertonic saline group, we suggest that the povidone iodine is not the best protoscolicidal agent.

Conclusion

Usage of 10% povidone iodine as a protoscolicidal agent carry high risk of sclerosing cholangitis.

Recommendations

More prospective studies are required to evaluate the safety of povidone iodine usage as a scolicidal agent in other different concentrations as well as different animal models.

Limitations

Preparation of twenty guinea pigs and maintaining their survival at operation and four months after.

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