Non-surgical Ablation of the Gall bladder: An Animal Study

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Stone recurrence is one of the major drawbacks of any non-surgical treatment of gall bladder stones. Ablation of the gall bladder would alleviate this risk. In the present research we evaluated different chemical agents in respect to their ability to destroy completely the gall bladder mucosa of the rabbit with subsequent obliteration of its lumen. We found that absolute alcohol caused total necrosis of the mucosa after continuous contact for 10 minutes in all animals studied. This was followed by growth of granulation tissue from the wall into the gall bladder lumen. The lumen was totally obliterated in 50% of the animals studied after 8 weeks. Methyl-tertiary-butyl ether is less potent in causing mucosal destruction; 50% dextrose does not cause permanent damage to the mucosa.

Cholelithiasis is one of the most common surgical illnesses. Cholecystectomy is the standard treatment for gallstones. Recently, there has been great enthusiasm in undertaking trials on non-surgical methods for the treatment of cholelithiasis. Oral bile acid medication, lithotripsy, contact dissolution via percutaneous cholecystostomy and percutaneous mechanical extraction alone or in combination are being pursued.

One of the major limitations for the widespread acceptance and use of such non-surgical treatment modalities for gall bladder stones is the problem of stone recurrence. After bile acid treatment the recurrence rate ranges between 10 and 50%. Comparable rates should be expected for the contact dissolution and lithotripsy, although follow-up times are too short to allow definite judgement.

 Destruction of the gall bladder mucosa with obliteration of its lumen would alleviate the risk of stone recurrence completely. This approach is being investigated, but until now only a little work has been published on it. This experimental study evaluates the efficacy of absolute alcohol, methyl-tertiary-butyl-ether (MTBE) and 50% dextrose in destroying the gall bladder mucosa with subsequent obliteration of its lumen.

Materials and Methods

White rabbits weighing 3–4 kg were used. General anaesthesia was achieved using ketamine as the sole agent (Ketalar® 50 mg/kg im). An upper midline laparotomy was performed and the liver lobe carrying the gall bladder...
was identified and pulled out to the surface of the wound. The cystic duct was identified and ligated with a 3/0 catgut tie. Using a 16G needle the gall bladder was punctured transhepatically and the bile aspirated completely. Then one of the three above mentioned chemicals was injected through the same needle until full distension of the gall bladder was achieved. The chemical was aspirated 10 min later and the wound closed in layers using a 0-chronic suture. In one group of animals no chemical was injected after bile aspiration. As control, we performed laparotomy on a group of animals where no other procedure was done apart from identification and palpation of the gall bladder (see Table 1). The animals were sacrificed 1, 4 or 8 weeks postoperatively.

At sacrifice the liver was removed in continuity with the extrahepatic biliary tree and duodenum and fixed in buffered formalin. After fixation for at least 24 h, serial sections were obtained from the duodenum, the papilla of Vater, common bile duct, cystic duct and gall bladder and random sections from the liver and were stained with haematoxylin and eosin.

Blood was taken preoperatively, on the first postoperative day and at sacrifice. The following parameters were measured: total protein, albumin, glutamic oxaloacetate transaminase (GOT), glutamate pyrovate transaminase (GPT), alkaline phosphatase (ALK) and bilirubin. All data were compared with basic values. Student’s t-test was used for statistical analysis.

Results

The means of the biochemical parameters were not significantly different from the preoperative values in any of the experimental groups on the first postoperative day or at sacrifice. At sacrifice, all animals showed macroscopically minimal adhesions with the omentum in the area of the gall bladder. The microscopic examination of the liver showed in all groups minimal to mild fatty metamorphosis, mainly adjacent to the gall bladder. The common bile duct, the ampulla of Vater

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of animals</th>
<th>Procedure</th>
<th>No. of animals sacrificed after</th>
<th>1 week</th>
<th>4 weeks</th>
<th>8 weeks</th>
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<tr>
<td>I</td>
<td>8</td>
<td>Laparotomy only</td>
<td>3</td>
<td>0</td>
<td>5</td>
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<tr>
<td>II</td>
<td>8</td>
<td>Laparotomy, cystic duct ligation, aspiration of bile</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>III</td>
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<td>As group II but with injection of absolute alcohol</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>20</td>
<td>As group II but with injection of MTBE</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>10</td>
<td>As group II but with injection of 50% Dextrose</td>
<td>5</td>
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<td>0</td>
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Figure 1. Normal gall bladder mucosa. (Magn. 10 x 10).

and duodenum showed no histologic abnormality. The findings in the gall bladder will now be discussed in detail for each group.

Group I (Laparotomy only)

No macroscopic or microscopic abnormality was found (Fig. 1).

Group II (Laparotomy, cystic duct ligation and aspiration of bile)

At 1 and 4 weeks the gall bladder was always distended and contained mucoid material. Histologically flattened but otherwise intact mucosa was found (Fig. 2). At 8 weeks the gall bladder was rather small and contained thickened greenish material, in one specimen, it was like a small soft stone. Histologically only flattened epithelium was seen.

Group III (As Group II but with the injection of absolute alcohol)

All specimens showed macroscopically a collapsed gall bladder. Histology showed at 1 week total necrosis of

Figure 2. Flattened, otherwise intact gall bladder mucosa. (Magn. 10 x 4).
the mucosa extending into the muscularis layer and a preserved lumen (Fig. 3). At 4 weeks there was beside the total necrosis granulation tissue growing from the wall into the still present lumen. In one of the five specimens the lumen was already obliterated by granulation tissue. At 8 weeks, five specimens showed complete obliteration of the lumen (Fig. 4). The remaining five specimens showed more pronounced granulation tissue than at 4 weeks but a lumen was still present.

**Group IV (As Group II but with the injection of methyl tertiary butyl ether)**

The gall bladder was always collapsed except in one specimen. At 1 week there was total necrosis of the mucosa in two specimens. In the other three specimens extensive necrosis was observed but there were multiple areas of intact mucosa. At 4 weeks three specimens showed total necrosis with starting granulation tissue. The other two specimens showed again islands of intact mucosa in different areas of the wall. At 8 weeks there was marked proliferation of granulation tissue in six specimens showing total necrosis of the mucosa. In three other specimens there were again islands of intact mucosa present. One specimen showed intact flattened epithelium with intact lumen. This gall bladder was macroscopically distended. Complete obliteration of the lumen was not observed in any specimen.

We could not observe any regenerating epithelium at the area of the cystic duct ligation in any specimen of Groups III or IV.

**Group V (As Group II but with injection of 50% dextrose)**

The gall bladder was macroscopically of normal size and contained mucoid material. Histologically all specimens obtained after 1 week showed areas of haemorrhage in the submucosal and muscular layers with superficial ulceration in the mucosa with reactive atypia in the epithelial lining. Specimens obtained after 4 weeks showed still some haemorrhage in the wall of the gall bladder. The mucosa was flattened and showed no ulceration or granulation tissue.

**Discussion**

The results of this study show that absolute alcohol completely destroyed the gall bladder mucosa after 10 min of continuous contact in all animals studied. This destruction was followed by early growth of granulation tissue from the remaining layers of the wall. Already 8 weeks after instillation of the chemical the lumen was histologically totally obliterated in 50% of the specimens. No regenerating activity of the epithelium was observed. Salomonovitz\(^{10}\) reported earlier on complete mucosal destruction using absolute alcohol in four of six animals followed up only for 2 weeks. Getraudman\(^{11}\) used a mixture of 95% ethanol and either 2M% trifluoroacetic acid (TFA) or 5M% TFA for 15 min and found after 6 weeks sclerosis and fibrosis of the gall bladder in 92% of his animals. Our results show that no addition to the absolute alcohol is needed to obtain total mucosal destruction of the gall bladder; MTBE is far less potent and therefore not advisable as sclerosing agent. From our study of gallstone dissolution in human beings using MTBE we know that no permanent damage to the gall bladder occurs; 50% dextrose does not result in any significant mucosal destruction.

The time needed until complete obliteration of the gall bladder occurs depends obviously on the size of the gall bladder and the remaining lumen at the end of the procedure. Theoretically one could shorten this time by placing a suction catheter into the gall bladder after aspiration of...
the chemical. Trials to do so in the rabbit failed technically because of the very small size of the gall bladder. We are therefore repeating this experiment on larger species. We feel that shortening the time for total obliteration of the lumen is important when thinking of implementing the procedure on humans.

One of the main problems to be solved is the fail-safe occlusion of the cystic duct. Ligation of the duct would require surgical intervention. Application of a haemoclip is reported by Getrajdman\(^1\) so as not to prevent re-epithelialization of the lumen from the intact epithelium of the cystic duct. Cyanoacrylate occlusion of the cystic duct was successful, but not feasible for human trials as partial breakdown of the material was observed.\(^10\) Recently, Becker et al.\(^12\) reported on complete occlusion of the cystic duct in humans using endoluminal transcatheter electrocoagulation. We have been successful in placing a balloon catheter into the cystic duct in humans. If the time needed for obliteration of the lumen could be shortened by using suction in the gall bladder this balloon occlusion may be feasible for cystic duct occlusion until obliteration of the gall bladder occurs.

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**References**