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Intravenous Bile Salts Indication in Gallbladder Transparent Stones and Colicky Pains

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Abstract:- The role of UDCA in gallstones resolution has been widely debated and it is still a longstanding primary treatment of this syndrome. We explored on 20 patients both sex, randomly assigned, the feasibility, advantages, and drawbacks of intravenous high UDCA dosages intravenous perfusion compared with the same amount of bile salt oral delivery.

The primary clinical endpoint was stones disappearance and the surrogate endpoint was the relieve of colicky pain symptoms and liver enzymes improvement.

Notwithstanding the bias due to small cases number, the evidence is definitely in favor of parenteral treatment which is very effective especially in the acute control of pain, vomitus and nausea, when oral drugs and feeding is not advisable.

I. INTRODUCTION

The main risk factors for gallstones in the western population have been well identified: prolonged fasting, rapid weight loss, total parenteral nutrition, and drugs (somatostatin, and similar) treatment. In the cholesterol radiolucent gallstones affected patients, either asymptomatic or symptomatic, treatment with the hydrophilic bile salt ursodeoxycholic acid (UDCA) reduces the risk of biliary colic and mechanical complications such as acute cholecystitis and acute pancreatitis, but unfortunately the oral administration of this Bile acid cannot start during the acute phase of the colicky pain because of the adverse intestinal conditions with nausea, vomitus, gastro paresis, meteorism etc.

Due to this oral delivery gap, we challenged the parenteral administration of UDCA at high dosages, in order to keep the control of the symptoms as soon as possible and to trigger a rapid clearance of the cholesterol sludges and microaggregates that are responsible of bile and pancreatic ducts obstruction and infectious cholecystitis.

II. MATERIALS AND METHODS

20 patients volunteers (<12 males and 8 females), coming from the emergency Dept., aged between 35 and 65 years, appealed to our "Second Opinion Medical Consulting Network, Medical Centre (Modena, Italy), because of sudden burst of biliary colicky pain due radiolucent gallstones, diameter 0,3-0,9 mm and altered liver enzymes, some of them also icteric complaining of quite an intense pain with nausea and vomiting but without fever, negative inflammation markers (ESR, CRP) and slight leukocytosis, no rebound tenderness at the gallbladder manual exploration **(TABLE 1)**.

Tab. 1: Baseline Characteristics of study groups

Baseline Characteristics	Parenteral bile salts therapy Group (n=10)	Oral bile salts therapy Group (n=10)
Number patients	10	10
Age (years)	30-55 yrs	35-65 yrs
Female gender	6	4
Male gender	4	6
BMI (Body Mass index kg/m2)	29.06±4.6	28.18 ±3.8

Table 1

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The Second Opinion Medical Network is a consultation referral web and Medical Office System recruiting suddenly a wide panel of real-time available specialists, to whom any patient affected by any disease or syndrome and not adequately satisfied by the diagnosis or therapy can apply for an individual clinical audit **[1]**. Due to the doctor-patient communication gap, most of the patients usually wander around the medical websites looking for proper answers to their health problems. However, their search often becomes compulsive and obsessive and often ambiguous and frustrating **[2]**. Palmieri et al. **[3]** describe this borderline or even pathological behavior as the "Web Babel Syndrome" – a psychological imbalance affecting young and elderly patients, especially those with multiple synchronous diseases who receive from their caregivers heterogeneous and misleading information or advices, including confused, contradictory statements and prescriptions **[4]**. To deal with this problem, the Second Opinion Network aims to be a useful "problem-solving" support revisiting each diagnostic and therapeutic step and properly re-addressing tailored treatments and prognoses, as well as preventing unnecessary investigational procedures and unhelpful and expensive medical and surgical interventions **[5]**.

All the patients were visited and informed during a personal interview, gave their permission, and signed an informed consent.

The majority of them was not aware of having any biliary or liver problems but total cholesterol level an LDL had been high (more than 200 mg%) in lab exams performed in the last 24 months, without any medical or nutritional treatment; generally the biliary colic started a few hours after an abundant meal with cold beverages (wine and beer).

We excluded from the study severely obese people, diabetes, kidney insufficiency, major cardiovascular problems, compulsive eating or drinking. The recruited patients were asked to withdraw any medication either nutraceutical or chemical drugs, except antihypertensive.

Before starting the trial, each patient was clinically examined, history recorded, and submitted to echographic examination in order to evaluate the liver and gallbladder morphology, and the volume size, and location of the stones, cholecystic-cholangiography completed the study, in order to rule out calcium or calcium-cholesterol mixed stones.

The patients were explained the therapeutic protocol and signed an informed consent and authorization to the study, that had been previously supervised and approved by the local Academic clinical trials committee.

Parenteral UDCA had been supplied by SALF. S.p.a. (Cenate Sopra, Bergamo, Italy), a National Company regularly authorized to produce parenteral medications, either for TPN, or intravenous fluid support.

The UDCA bottles contained 3500 gr/lt and had to be perfused in a couple of hours.

A. We infused 3500 mg UDCA intravenously from a cubital vein every 12 hours for 6 days; the very first infusion at the admission was added with 20 mg hyoshine-N-butyl bromide and 75 mg diclofenac being the patients severely distressed by excruciating pain.

At the end of the week, when the colic pain had completely subsided, they were subdivided in two groups, comparable as to age, sex, single or multiples stones size (less than 1cm) and were and adequate, post prandial rest. The first group received 0,7 gr/kg oral UDCA accordingly with the standard literature upper effective dosage for three months.

The second group followed up with intravenous perfusion 3500 mg in 500 ml twice a week along the same period for three months (24 infusions total).

All the patients were admitted once a week for a visit and to update the record of their clinical history, enclosing new colicky events, adverse effects of the treatment.

III. RESULTS OF THE FIRST WEEK INTENSIVE TREATMENT (PARENTERAL GROUP)

The colicky pains were controlled by the first intravenous treatment in which a symptomatic therapy:
1 ampoule of antispasmodic hyoscine- N-butyl bromide (20 mg) and diclofenac (75 mg) were added.

The colics never relapsed along the week, and the patients felt much better since the second day of the therapy when they re-started oral feeding; no adverse effect of the parenteral treatment were recorded.

The pre-versus post-treatment lab exam, showed recovery of the liver function and downstage in of the bilirubin levels to normal.

IV. RESULTS OF THE ORAL VERSUS PARENTERAL TREATMENT IN THE FOLLOWING TRIMESTER

In the oral group, the colicky pain reappeared in 4 patients out of 10, during the first 40 days, but not in the intravenously treated group at the echographic evaluation total gallstones dissolution was evident in 7 of the parenteral, and in 3 of the oral UDCA group **(FIG.1)**.

In the parenteral group the remaining 4 patients showed reduction of the sludging concretions and overall stones volume more than 50% compared with the pre-treatment imaging; in the oral UDCA group the remaining patients showed less than 30% average stones volume reduction. The general clinical conditions were excellent without any untoward effect of the oral or parenteral UDCA treatment **(TABLES 2-3)**.

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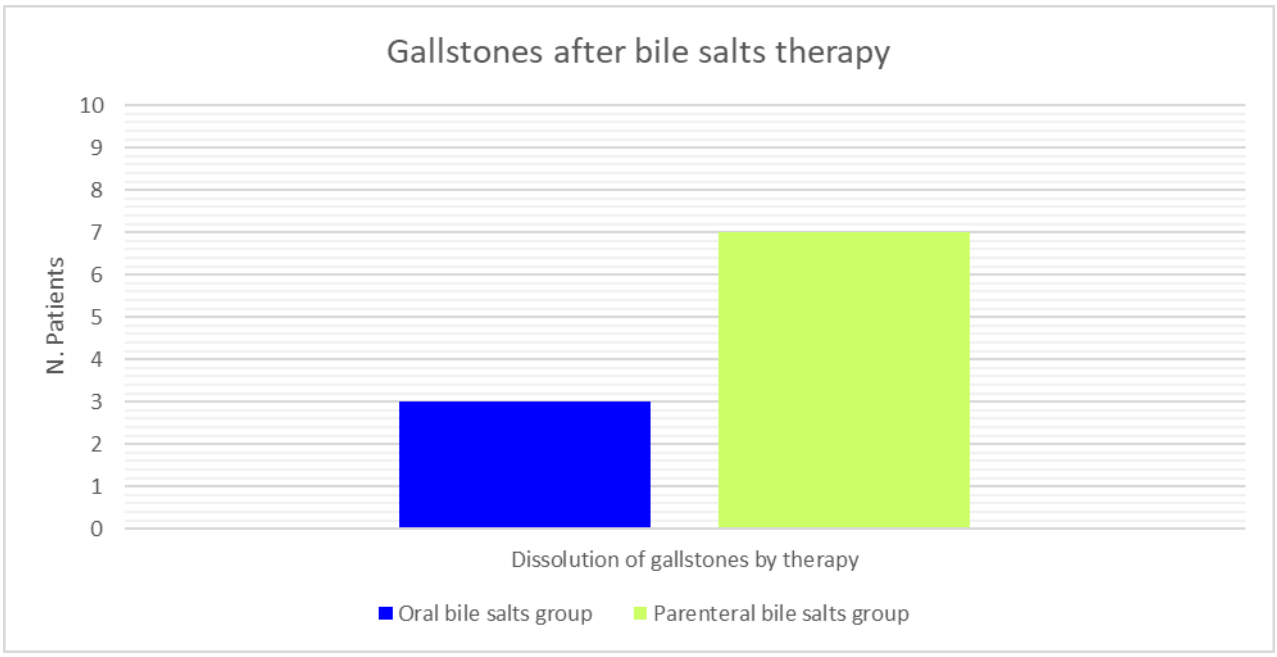

Fig 1:- Graphic representation of gallstones dissolution in bile salts groups after treatment

TAB.2: LIVER PARAMETERS IN PARENTERAL BILE SALTS GROUP (N=10)

N.	PAT.	AGE (yrs)		AST (U/L), range (8-48)		Alanine transaminase -ALT (U/L) range (7-55)		Alkaline phosphatase -ALP (U/L), range (40-129)		Gamma-glutamyl transferase-GGT (U/L), range (8-61)		Bilirubin (mg/Dl), range (0.1-1.2)	
				PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
#1	P.G.	63	Mult.stones max 0.8 mm	180	52	118	75	150	49	121	18	4.7	1.1
#2	B.L.	46	Biliary sludge microst.	124	91	102	60	141	60	139	52	5.0	1.1
#3	P.M.	59	Mult. Stones chol 0.5 mm	89	53	156	58	137	54	141	32	4.8	1.7
#4	F.M.	44	Single stone 0.6 mm	71	49	120	55	120	62	157	31	4.7	1.5
#5	T.S.	52	Mult stones 0.6 mm	73	33	170	43	127	42	168	29	4.6	1.5
#6	R.A.	55	Gall blad. Full	93	39	153	52	139	63	181	13	4.9	1.5
#7	F.E.	75	Mult stones, 0.4 mm	60	31	107	67	167	81	189	10	4.8	1.5
#8	C.J.	43	3 stones 0.7	112	67	173	62	188	49	191	29	5.0	1.5
#9	P.G.	47	Mult stones+sludge	75	14	195	30	199	96	137	12	4.7	1.0
#10	F.M.S.	39	single stone 1 cm	143	78	109	39	203	72	164	31	4.5	1.8

Table 2:- Liver parameters in parenteral bile salts group (n=10)

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TAB.3: LIVER PARAMETERS IN ORAL BILE SALTS GROUP (N=10)

N.	PAT.	AGE (yrs)		Aspartate transaminase -AST (U/L), range (8-48)		Alanine transaminase -ALT (U/L) range (7-55)		Alkaline phosphatase -ALP (U/L), range (40-		Gamma-glutamyl transferase-GGT (U/L), range (8-61)		Bilirubin (mg/Dl),range (0.1-1.2)	
				PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
#1	F.F.	37	Multiple stones 0.5 mm	87	41	165	56	179	102	149	12	5.0	1.2
#2	G.E.	37	Gallbladder and choled stones 0.4-0.7 mm	101	45	105	42	210	113	135	11	4.9	1.2
#3	G.N.	32	Microlith gallbladder	165	86	179	52	160	95	127	24	4.8	1.5
#4	L.F.	36	4 stones 0,5 mm	99	85	153	44	182	126	110	19	4.75	1.5
#5	L.R.	46	Bile sludge + stone 0.5 mm	108	39	168	47	220	104	124	48	4.99	1.7
#6	L.P.	51	Multiple stones gallbladded	156	27	165	51	173	53	130	38	4.56	1.7
#7	L.W.	62	Microlithiasis + single stone	130	79	160	48	164	47	113	42	4.91	1.4
#8	M.T.	51	Multiple stones 0.6-0.9	112	68	150	63	191	89	107	18	5.01	1.1
#9	M.E.	29	3 stones 0.7-0.9 mm	115	63	137	51	186	95	118	57	4.96	1.5
#10	M.A.	58	Multiple stones	99	49	112	49	158	99	123	58	5.1	1.3

Table 3-: Liver parameters in oral bile salts group (n=10)

V. DISCUSSION AND CONCLUSION

The colicky pain episodes due to gallstones must be carefully observed and treated, not only to relieve the patient heavy discomfort, but specifically to avoid complications such as cholecystitis, pancreatitis, and liver function impairment. UDCA is the gold standard therapy of the gallstones since the first Japanese clinical study and the most effective oral dosage from a metanalysis of 23 previous trials (performed from 1966 to 1992) published in 1993, has been fixed in 7-10 mg UDCA/ kg /day for a minimum of 6 months **[6]**.

Successful litholysis depends by individual physio pathological conditions but mainly by the stone diameter, being the optimal target less than 0,5 cm, and progressively inferior up to 1 cm:

- Obesity,
- Gallbladder wall dysfunction with reduced contractility and mucosa abnormalities,
- Gallstones structure not purely cholesteric but variably contaminated with calcium salts,
- Biliary/dyspeptic recurrent symptoms

Reduce the probability and percentage of stones clearance by UDCA treatment.

UDCA has a direct downstaging role upon gallbladder wall inflammation and contractile dysfunction. In fact, during gallstone storage, myocites increase the level of oxygen species [ROS and prostaglandin E2 (PGE2)] with enhanced lipid peroxidation and reduced receptors of cholecystokinin (CCK-8), PGE2 and potassium chloride. Moreover UDCA, reducing the excess cholesterol and "neutralizing" the hydrophobic bile acids, restores the balance between aggressive biliary factors and gallbladder protective mechanisms **[7].**

Data emerging from this study, reveal the occurrence, in gallbladders surgically removed from patients with cholesterol gallstones, of an increased number of macrophages in the muscle layer when compared to the normal gallbladder. Guarino et al **[8]**, in a double blind randomized 4-wk study, compared the effects of UDCA with those of placebo in patients with symptomatic gallbladder stones, scheduled to undergo cholecystectomy, and showed that this hydrophilic bile acid leads to a decrease in the number of activated macrophages in the muscle layer and to the reduced production of PGE2 in the gallbladder muscle. PGs are catalytic products of cyclooxygenase-2 (COX2) and are well-known modulators of gastro-intestinal smooth muscle function **[9-10]**. UDCA anti-inflammatory action upon the stones harboring gallbladder wall is expressed by the reduction of activated macrophages which are the main source of PG production.

In our study, the intravenous approach has been necessarily proposed in the acute phase of the colicky pain, just when oral medications cannot be administered, the patient is fasting with nausea and vomiting (with subsequent hydro electrolyte imbalance) and complications have urgently to be prevented (especially acute cholecystitis and pancreatitis) in old weak, frail, sick people with high, mortality risk either in surgical or conservative perspective.

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A. The intravenous UDCA treatment (potentiated, but only once, at the beginning by antispasmodic ant inflammatory drug support) was able to remit steadily the colicky episodes, and to improve and normalize the liver function as well as the patient conditions

The high dosage administered not only has been safe and uneventful, but certainly increased the bioavailability of UDCA, through the enterohepatic recirculation engaging the whole liver parenchyma in:

- Reducing the biliary secretion of cholesterol,
- Strongly increasing the mycelial solubilization of cholesterol in the bile fluid by expansion of the circulating bile acids pool,
- Inducing a highly effective cholesterol solubilizing liquid/crystal mesophase.

This explains also the best results achieved prolonging the intravenous UDCA therapy along 3 months with total remission of bile colics and higher total or partial stones dissolution rate, compared with the orally treated group: this latter, with high probability took advantage from the first week aggressive parenteral approach, and the strong bile acids pool expansion but the switch to the UDCA capsules probably reduced the benefits and delayed the results, compared with the group submitted to prolonged intermittent.

Parenteral therapy: this explains some relapsing colicky episodes and less smart litholytic effects along the three months of UDCA oral treatment.

Conclusively, we claim the necessity of regular availability of a second UDCA administration route in emergency setting, for the patients admitted with acute colicky gallstones pain in which oral treatment is temporarily contraindicated, confirming that the intravenous infusion is safe and definitely effective to reduce the patient's life, risks of complications, his pain and sufferance and cut the hospital costs ruling out complications and prolonged hospital stay.

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