The Effect of Aspirin on Gallbladder Volume in Patients with Acute Cholecystitis: "Ultrasonographic Study"

AKUT KOLESİSTİTLİ HASTALARDA ASPİRİNİN SAFRA KESESİ VOLÜMÜNE ETKİSİ: "ULTRASONOGRAFİK ÇALIŞMA"

Sait KAPICIOĞLU*, Ömer ŞENTÜRK**, Mehmet SARI*, Abdülhalim BAKİ*

* Dept. of Internal Medicine, Section of Gastroenterology, Medical School of Karadeniz Technical University, Trabzon
** Social Security Hospital, İstanbul, TURKEY

Summary

Prostaglandins (PGS) are important mediators in the pathogenesis of the acute cholecystitis. We, therefore, decided to study the effect of aspirin on gallbladder volume and pain-reliving capacity in patients with acute choleciystitis. Ten patients with acute cholecystitis and ten healthy subjects participated in this study. The gallbladder volumes were measured using ultrasonography. Pain relief was defined as a reduction in severity from grade 3 or 2 (severe or moderate) to 1 or 0 (mild or none). After fasting the baseline measurement was taken. The patients and volunteers received lg aspirin with 50 ml water orally. Two hours later the gallbladder volumes were rescanned in 15 min intervals for 60 min. The baseline gallbladder volumes of the healthy subjects were 19.5±5.2 ml. The mean baseline gallbladder volume of patients with acute cholecystitis was greater than that of the control goup (35.0±6.4 ml). This difference was not statistically significant. After administration of aspirin significant changes in the gallbladder volume were observed. In patients with acute cholecystitis the fasting gallbladder volumes increased by 35.2%-62.8% compared to the baseline (p<0.01-0.001) and by 132.2%-196.9% compared to the control group (p<0.01-0.001). Aspirin was significantly effective in reducing pain when compared against pretreatment in the 1st hr. The mean pain grade was 1.80±0.92 in baseline and 0.00±0.00 after treatment (p<0.007).

In conclusion, aspirin significantly increased gallbladder volume in patients with acute cholecystitis. Patients were totally free of pain after treatment with aspirin. Aspirin may prevent on the reliefbiliary colic due to acute cholecystitis.

Key Words: Acute cholecystitis, Gallbladder volume, Aspirin

T Klin J Med Res 2001, 19:109-113

Özet

Prostaglandinler (PGs) akut kolesistit patogenezinde önemli mediatörlerdir. Bu çalışmada akut kolesistitli hastalarda aspirinin safra kesesi volümü ve ağrı üzerine etkisi araştırıldı. Çalışmaya 10 akut kolesistitli hasta ve 10 sağlıklı birey alındı. Safra kesesi volümleri ultrasonografik olarak ölçüldü. Ağrının rahatlaması, şiddetinin 3 veya 2'den (şiddetli veya orta şiddette) 1 veya sıfıra (hafif veya hiç yok) inmesi ile tanımlandı. Bazal ölçüm açken yapıldı. Hastalar ve sağlıklı bireyler 1 gr aspirini 50 ml su ile aldılar. İki saat sonra 15 dakika ara ile safra kesesi volümü 60 dakika boyunca ölçüldü. Sağlıklı bireylerde bazal safra kesesi volümü sağlıklı bireylerde 19.5±5.2 mi, akut kolesistitli hastalarda ise (35.0±6.4 ml) kontrolden fazla idi. Fark istatistiksel olarak anlamsızdı. Aspirin alan akut kolesistitli hastalarda safra kesesi volümü bazal volüme göre %35.2-%62.8 (p<0.01-0.001), kontrole göre %132.2-%196.9 (pO.Oİ-0.001) kadar arttı. Bazal ağrı derecesi 1.80±0.92 iken tedavi sonrası 0.00±0.00 idi (p<0.007).

Sonuç" olarnk, aspirini:' 'ikylî ItöU^lstiİ'i'' ^ifsa Vesesî-Sonuç olarak, aspirinin akut kolesistitte safra kesesi volümünü anlamlı derecede arttırdığı gözlendi. Aspirin tedavisinden sonra ağrı tamamen kayboldu. Bu sonuçlar aspirinin akut kolesistit ve komplikasyonlarına bağlı bilier kolikte ağrının azaltılmasında yararlı olabileceğini düşündürmektedir.

Anahtar Kelimeler: Akut kolesistit, Safra kesesi volümü, Aspirin

T Klin Araştırma 2001, 19:109-113

Received: Feb. 25, 2000

Correspondence: Prof.Dr. Sail KAPICIOGLU
Dept. of Internal Medicine,
Section of Gastroenterology,
Medical School of
Karadeniz Technical University
61080 Trabzon - TURKEY

Prostaglandins (PGs) are important mediators in the inflammatory process (1) and are also synthesised by inflamed gallbladder (2), cause contraction of gallbladder muscles (3,4) and can induce net fluid secretion of the gallbladder mucosa (4,5). Also the ability to change PG formation by inhibi-

tion of PG synthetase activity with aspirin and other non-steroidal anti-inflammatory agents (NSAID's) is important in the treatment of any disease with an inflammatory component. An endogenous PG biosynthesis in the gallbladder wall, induced by mechanical or chemical trauma, might explain a prolonged increase in intraluminal pressure. The severe the inflammation was, the greater were the prostanoid levels (6). Furthermore, prostaglandin E2 (PGE_2) was identified in the gallbladder contents in the cases of acute cholecystitis and in response to distention of the normal gallbladder (7). Investigators have shown that though gallbladder motility in patients with gallstones is enhanced by NSAID's it is not altered in healthy volunteers (8-11). It would be important to know if the beneficial effect of NSAIDs on gallbladder contractility is seen in the patients with acute cholecystitis also. We, therefore, decided to study the effect of aspirin on gallbladder volume and pain-reliving capacity of the patients with acute cholecystitis.

Material and Methods

Ten patients with acute cholecystitis and ten healthy volunteers agreed to participate in the study. The trial was performed in accordance with the Declaration of Helsinki. Ethics Committee Approval was obtained where appropriate, and witnessed. Informed consent was obtained from each patient prior to the study. The patients' average age was 52.3±4.6 range (42-62) years. The healthy volunteers' average age was 45.6±8.3 (29-61) years and was not different from the patients with acute cholecystitis. All patients had fever, leucocytosis, Murphy's sign and an oedematous gallbladder as proved by ultrasonography. Patients with gastroduodenal ulcer disease or with severe cardiopulmonary disease were excluded from the study. All patients remained in the emergency ward for a period of 24 hrs. After physical, laboratory and ultrasonographic investigations, their pain levels were determined in order to compare initial and altered test pain. Those with moderate or severe pain (grade 2 or 3 on the rating scale) described by the treatment regimen were evaluated on the basis of the four- point scale as previously described (12). 0 for no pain, 1 for mild pain, 2 for moderate pain, and 3 for severe pain. The presence or absence of other symptoms such as nausea, vomiting, fever and use of rescue medication were also noted. The patients were given no medication, and gastric tube for gastric decompression. The primary endpoints for clinical efficacy were the relief of pain from grade 3 or 2 to grade 1 or 0 within 12 hrs. after treatment. These were defined as any untoward clinical sign or symptom that occured or worsened after treatment. The gallbladder volumes were measured using ultrasography (13). Using a 3.5 or 5 MHz transducer, real time ultrasound scans were obtained with Siemens Sonoline SL 2 3.5 Mhz. The subjects were scanned supine in the right anterior oblique position by a radiologist experienced in ultrasonography. The gallbladder was visualised in the longitudinal and transverse planes, and measurements of maximum length, width and height were taken in duplicate. The gallbladder volume was subsequently calculated using the ellipsoid formula (Volume = 0.52 * length * width * height).

Scans were performed after fasting for 12 hours to establish the baseline values. Then both groups (healthy volunteers and patients with acute cholecystitis) received 1 g aspirin (Bayer) with 50 ml water orally. Two hours later the gallbladder were rescanned in 15 min intervals for 60 min.

The results are expressed as mean ± SEM, and were analysed initially by the Mantel- Haenszel X^2 and Mann Whitney-U or Wilcoxan signed Rank tests.

Results

Demographic and clinical details are summarized in Table 1.

The mean baseline gallbladder volume of the control group was 19.5±5.2 ml. In the acute cholecystitis group the mean baseline gallbladder volume was higher than in the control group (35.0±6.4 ml). This difference was not statistically significant. After administration of aspirin, significant changes in gallbladder volume were observed. In patients with acute cholecystitis the fasting gallbladder volume increased by 35.2%-62.8% compared to the baseline ($p<0.01$-0.001). Figure 1, Table 2; pain relief defined as reduction in severity from 3 or 2 to 1 or 0. Aspirin was significantly effective in reducing pain as compared to the pretreatment in the 1st hrs. The mean pain grade was

Table 1. Patient demographies and pretreatment characteristics of the acute cholecystitis

Characteristics	No (%)
No	10
Sex	
Male	3(30)
Female	7(70)
Mean age(years)	52,3±4,6
Pretreatment severity	
No pain	0(0)
Mild	2(20)
Moderate	6(60)
Severe	2(20)
Stone	9(90)
Non-stone	1(10)
Obesity	
BM1>12%	1(10)
BMI<12%	5(90)

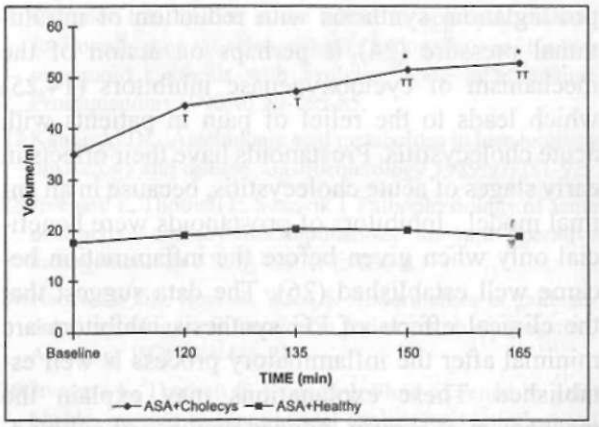

Figure 1. Effect of aspirin on healthy subjects and in patients with acute cholecystitis
*p<0.01, **p<0.02, difference from baseline
^{T}p<0.01, ^{TT}p<0.001 difference from control

1.80 ± 0.92 in baseline and 0.00 ± 0.00 after treatment (p < 0.007) (Figure 1).

The effect of aspirin decrease in pain level, could be detected after just 1 hr. No major side effects were recorded during aspirin treatment.

Discussion

This study demostrated that aspirin significantly increased gallbladder volume of patients with acute cholecystitis. Aspirin was effective in providing with pain-relief in the patients with acute cholecystitis (reduction from grade 3 or 2 to grade 0) for 12 hrs. They were all totally free of pain after the treatment with aspirin. Our results agreed with previous studies (14-18).

PGs have a physiological role in the maintenance of the motility of gallbladder musculature (8-11) and play a central role in the pathogenesis of both calculous and acalculous cholecystitis. Increased production of PGs by the inflamed human gallbladder has been demonstrated in vitro (7) and in vivo (6,19,20). The severe the inflammation was, the greater were the prostanoid levels (6,21). Furthermore, PGE_2 was identified in the gallbladder contents in cases of acute cholecystitis and in response to distention of the normal gallbladder (7). Experimentally instillation into the gallbladder lumen causes changes which increase mucosal PGE_2 levels and induce acute cholecystitis (22) because the changes brought about cyclooxgenase inhibitor indomethacin (19).

Prostaglandins induce active fluid secretion by the gallbladder mucosa (4,23). Exogenous administration of PGE_2 induces a secretory response by the gallbladder, epithelium, with stimulation of mucus secretion and contraction of the gallbladder wall (4) This active secretion by the gallbladder mucosa is abolished by PG synthetase inhibitor (24). Cessation of fluid secretion by inhibition of

Table 2. Effect of aspirin on healthy subjects and in the patients with acute cholecystitis.

		The mean value of gallbladder volume after administration of aspirin (time-min)				
Groups	No	Baseline	120	135	150	165
Asa+Cholecystitis	10	35.0±6.4	44.5±11.5	47.3±12.2^{T}	51.5±10.9*^{TT}	52.8±13.0**^{TT}
Asa+Healthy	10	19.5±5.2	19.07±12.2	20.3±10.7	20.1±11.3	18.9±10.1

*p<0.01, **p<0.02, difference from baseline
^{T}p<0.01, ""pO.OO1 difference from control

prostaglandin synthesis with reduction of intraluminal pressure (24) is perhaps on action of the mechanism of cyclooxygenase inhibitors (14,25) which leads to the relief of pain in patients with acute cholecystitis. Prostanoids have their effects in early stages of acute cholecystitis, because in an animal model, inhibitors of prostanoids were beneficial only when given before the inflammation became well established (26). The data suggest that the clinical effects of PG synthesis inhibitors are minimal after the inflammatory process is well established. These explanations may explain the mechanism of aspirin-induced increase of gallbladder volume and pain relief in the patients with acute cholecystitis.

The importance of fluid secretion in the development, of acute cholecystitis is supported by the observations that (1) the inflamed gallbladder secretes rather than absorbs fluid (27), (2) acute inflammation is only seen in animals that secrete fluid to the gallbladder lumen (28), and (3) a correlation exists between the rate of fluid secretion and the severity of the inflammation in animals (28) and patients (29). As noted before , implantation of a gallstone or insertion of a long-term indwelling catheter or instillation of lysolecithin the obstructed gallbladder induces continuous and active secretion of fluid into the gallbladder (30). In addition , the fluid secretion into the lumen of an inflamed or obstructed gallbladder is enhanced by feeding and reduced by fasting (31). This active secretion is abolished by PG synthetase inhibitor (19,24). Protective mechanisms may reduce net fluid secretion when the intraluminal pressure rises (28,31).

In conclusion this study demonstrated that aspirin significantly increases gallbladder volume in patients with acute cholecystitis. The patients were totally free of pain after the treatment with aspirin. These results suggest that aspirin may prevent the relief of biliary colic due to acute cholecystitis.

RFFFRFNCF^v REFERENCES

1. **FeiTO** SH. Prostaglandins. In Hock JC editor. Chemical messengers of the inflammatory response. Amsterdam 1979. Ellesmere. Biomedical Press, 113.
2. Wood JR, Stafford IF. Prostaglandins in chronic cholecystitis. Prostaglandins 1977;13: 97-107.
3. Niacin J, Cm Cloy RB, Gin AC, Nikon SK. Effects of prostaglandins E1-E2 andFl and pentagastrin on the gallbladder pressure in dogs. ER J Pharmacy 1975;30:107-12.
4. Thomell E, Svanvik J, Wood JR. Effect of intraarterial prostaglandin E2 on gallbladder fluid transport, motility and hepatic outflow in the cat. Scand J Gastroenterol 1981;16:1083-8.
5. Hints K, Gaits R, Koerlings H, Wood JR. Characterisation of the prostaglandins induced secretion in the isolated gallbladder of guinea pig. Nanny Schmiedebergs. Arch Pharmacy 1976;293: R 34.
6. Kaminski DL, Deshpande YG, Westfall S,Herbold D. Evaluation of prosttacyclin production by human gallbladder. Arch Surg 1989;124:277-80.
7. Kaminski DL, Deshpande Y, Thomas L, Qualy J, Blank W. Effect of oral ibuprofen on formation of prostaglandins E and F by human gallbladder muscle and mucosa. Dig Dis Sci 1985; 30:933-40.
8. O'Donnel LJD, Wilson P, Guest P, Catnach SM, Mclean A, Wickham JCA, Fairclough PD.Indomethacin and postprandial gallbladder emptying. Lancet 1992; 339:261-71.
9. Murray FE, Stinchcombe SJ, Hawkey CJ. Effect of indomethacin and misoprostol on fasted gallbladder volume and meal- induced gallbladder contractility in humans. Dig Dis Sci 1992; 37:1228-31.
10. Das A, Baijal SS. and Saraswat VA. Effect of aspirin on gallbladder motility in patients with gallstone disease. A randomized, double-blind, placebo-controlled trial of two dosage schedules. Dig Dis Sci 1995; 40:1782-83.
11. Janderko G, Janderko K, Konca A, Pelko M. Effect of a synthetic prostaglandin El derivative, misoprostol on fasted gallbladder emtying in man. Am J Gastroenterol 1989; 84:1375-9.
12. Huskinson EC. Measurement of pain. Lancet 1974; 2:1127-30.
13. Evasion GT, Bravar Man DZ, Johnson ML, Ken F Jar. A critical evaluation of real-time ultrasonography for the study of gallbladder volume and contraction. Gastroenterology 1980;79: 40-6.
14. Throttle E, Mansion R, Svanvik J. Indomethacin intravenously-A new way for effective relief of biliary pain: A double-blind study in man. Surgery 1981;70: 468-72.
15. Gladden G, Kahn PJ, Alone R, Wyznitzer T and Faces. Biliary colic treatment and acute cholecystitis prevention by prostaglandin inhibitor Dig Dis Sci 1989; 34: 809-11.
16. Babb RR. Managing gallbladder disease with prostaglandin inhibitors. Post Grad Med 1993; 94: 127-30.
17. Anez MS, Martinez D, Pacheco JL, Gonzales H, Rivera L, Pelaschier E, Uzcategui L, Romero MD, Molina Z, Roditti de Montilla M. Indomethacin in the treatmwnt of acute cholecystitis and biliary colic. GEN 1991;45,32-7.
18. Nilsson B, Delbro D, Hedin L, Friman S, Andius S, Svanvik J. Role of cyclooxygenase-2 for fluid secretion by the inflamed gallbladder mucosa. J Gastrointest Surg 1998; 2:269-79.
19. Thornell E, Jivegard L, Bukhave K, Rask-Madsen Jsvanvik J. Prostaglandin E2 formation by the gallbladder in experimental cholecystitis. Gut 1986;27:370-3.

20. Myers SI, Bartila L. Human Cholacystitis is associated with increased gallbladder prostaglandin 12 and prostaglandin E2 synthesis. Hepatology 1992;16:1176-9.

21. Kaminski DL, Deshpande YG, Thomas LA. The role of prostaglandin E and F in acute acalculocus cholecystitis. Hepatogastroenterology 1987;34:70-3.

22. Neiderhiser D, Thomell E, Bjork S, Svanvik J. The effect of lysophosphatidyl choline on gallbladder function in the cat. J Lab Clin Med 1983;101:699-707.

23. Heintzc K, Leinesser W, Petersen KU, Heidcnreich 0. Triphasic effect of prostaglandin E1, E2, and F2 on fluid transport of isolated gallbladder of guinea-pig. Prostaglandins 1975;9:309-22.

24. Thornell E, Jansson R, Svanvik J. Indomethacin reduces raised intraluminal gallbladder pressure in acute cholecystitis. Acta Chir Scand 1985;151:261-5.

25. Goldman G, Kahn PI, Alon R, Wiznitzer T. Biliary colic treatment and acute cholecystitis prevention by prostaglandin inhibitor. Dig Dis Sci 1989;34:809-11.

26. Myers SI, Haley-Russel D, Bartula LL, Nabzdyk W. Common bile ligation in the rabbit: an appropriate model for investigating the relationship of endogenous gallbladder prostanoid synthesis with evolving acute inflammation. Prostaglandins 1990;40:40-165-85.

27. Kaminski DL. Arachidonic acid metabolites in hepatobiliary physiology and disease. Gastroenterology 1989;97:781-92.

28. Jivegard L, Thomell E, Svanvik J. Pathophysiology of acute obstructive cholecystitis:implications for non operative menagement. Br J Surg 1987;74:1084-6.

29. Nahrwold DL, Rose R, Ward S. Abnormalites in gallbladder morphology and function in patients with cholecystitis. Ann Surg 1976;184:415-21.

30. Jivegard L, Thomell E, Svanvik J. Fluid secretion by gallbladder mucosa in experimental cholecystitis is influenced by intramural nerves. Dig Dis Sci 1987;32:1389-94.

31. Svanvik J, Pellegrini CA, Allen P, Bernhoft R, Way LW. Transport of fluid and biliary lipids in the canine gallbladder in experimental cholecystitis. J Surg Res 1986;41:425-31.