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Acute pain management in symptomatic cholelithiasis

Tahir Masudi, Helen Capitelli-McMahon, Suhail Anwar

Tahir Masudi, Helen Capitelli-McMahon, Suhail Anwar, York Hospitals NHS Foundation Trust, the York Teaching Hospital, North Yorkshire YO31 8HE, United Kingdom

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Correspondence to: Tahir Masudi, FEBS, MRCS, York Hospitals NHS Foundation Trust, the York Teaching Hospital, Wigginton Road, York, North Yorkshire YO31 8HE, United Kingdom. tahir.masudi@yahoo.com
Telephone: +44-7950-794197

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Abstract

AIM

To review the evidence for the use of different non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of biliary colic.

METHODS

The strategies employed included an extensive literature review for articles and studies related to biliary colic from electronic databases including PubMed, Science Direct, Wiley Inter Science, Medline and Cochrane from last 15 years. Keywords: "Biliary colic", "management of biliary colic", "non-steroidal anti-inflammatory drugs", "cholelithiasis" and "biliary colic management". Six randomized control trials, 1 non-randomized trial and 1 meta-analysis were included in this review. The outcomes of these studies and their significance have been reviewed in this paper.

RESULTS

Current evidence suggests there are no set protocols for biliary colic pain management. NSAIDs are potent in the management of biliary colic, not only in terms of symptom control but in disease progression as well. Apart from the studies on diclofenac and ketorolac, there are studies which have shown that intravenous tenoxicam and injectable flurbiprofen are equally effective in managing biliary colic. The efficacy of NSAIDs is superior in terms of lower number of doses and longer duration of action in comparison to other analgesic agents.

CONCLUSION

This literature review has found that NSAIDs are safe and effective for pain control in biliary colic, and reduce the likelihood of further complications.

Key words: Biliary colic; Management of biliary colic; Non-steroidal anti-inflammatory drugs; Cholelithiasis; Biliary colic management

Core tip: There are currently no set protocols for pain management in biliary colic. This literature review analyses studies from the last 15 years and shows that non-steroidal anti-inflammatory drugs (NSAIDs) provide safe

and effective pain control. It also suggests that NSAIDs play an important role in reducing the complication risk following episodes of biliary colic.

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INTRODUCTION

In developed countries, including United States, United Kingdom and other European countries, 10% of adults and 20% of people aged > 65 years have cholelithiasis. It is more than twice as common in females as in males[1]. Biliary colic is seen as a presenting symptom in 75%-80% of the patients with symptomatic cholelithiasis[2].

This review examines the evidence for the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesics in the management of pain in biliary colic as well as their role in the prevention of progression to complications.

MATERIALS AND METHODS

The strategies employed included an extensive literature search for articles and studies related to biliary colic from electronic databases including PubMed, Science Direct, Wiley Inter Science, Medline and Cochrane. The keywords used in electronic search were "biliary colic", "management of biliary colic", "non-steroidal anti-inflammatory drugs" and "biliary colic management". The literature searches of the last fifteen years brought up approximately 50 studies and papers in a variety of journals. However, only 6 randomized control trials (RCTs), 1 non-randomized trial and 1 meta-analysis fell within the purview of this review, which was to study the effects of NSAIDs and other pharmacological therapies on symptomatic cholelithiasis.

RESULTS

The studies were examined with the help of a questionnaire devised by the Critical Appraisal Skills Programme[3] recommended for evaluating RCTs in evidence-based medicine.

Akriviadis *et al*[4] designed a study investigating the effects of diclofenac in patients suffering from biliary colic. The study aimed to prove the benefits of diclofenac for pain alleviation, and also linked NSAIDS with preventing the development of complications related to cholelithiasis. The study involved 53 consenting patients who were known to have cholelithiasis and who were diagnosed with biliary colic. One group (n = 27) received 75 mg of 3 mL IM diclofenac and the other group (n = 26) received 3 mL of saline. The patients were followed up for 3 d and the effect of each treatment was gauged by changes in pain severity and progression to complications. Satisfactory levels of analgesia were obtained in 21 patients from the diclofenac group whilst only 7 from the placebo group were relieved of pain. Nearly 50% of the patients in the placebo group progressed to the development of acute cholecystitis. It was concluded that diclofenac usage could provide cost-effective pain relief in the acute phase of biliary colic and could also prevent development of subsequent complications.

This was a randomized, double-blind and controlled study. The inclusion criteria were based on the presence of right upper quadrant and epigastric pain. These patients were further subjected to sonography to demonstrate the presence of cholelithiasis. The exclusion criteria were strictly monitored. There was a longer follow-up of 3 d in these patients, which aided the adequate monitoring of responses to treatment and the recording of any complications in a surgical ward setting, thus minimizing the chances of observer bias and maintaining uniformity of care. The study also employed the setting up of end points which were based on patient response to treatment and time taken to get relief or symptom progression. This made it a well-controlled study keeping the wellbeing of patients paramount. This is a level-Ⅱ study with a sound aim and statistically significant results but the only limitation was the fallout of 28 patients from initial enrollment to the final conclusion.

Tomida *et al*[5] conducted an extensive study on the long-term use of ursodeoxycholic Acid (UDCA) therapy in patients with known cholelithiasis. The aim of this study was to evaluate the effects of this therapy on biliary pain and development of acute cholecystitis. The study included a cohort of 527 patients with uncomplicated cholelithiasis who were either given or withheld UDCA (600 mg/d). These patients were followed for 18 years and the results analysed. It was found that UDCA therapy was associated with reduced risk of developing biliary pain in symptomatic as well as in asymptomatic patients. The risk of conversion to surgery was also reduced in symptomatic patients treated with UDCA. On the basis of these findings it was concluded that UDCA therapy might be considered as a safe option in symptomatic patients and also in patients who carry a significant surgical risk.

This was a non-randomized prospective study designed to cover a large number of patients. The strengths of this study are that it had a large sample size and that the follow-up and data collection were uniform. The inclusion and exclusion criteria were strictly monitored and the allocation of an end-point meant that the patients were given a fair chance of getting an acceptable mode of management for their symptoms. However, the absence of randomization makes this a level-Ⅲ study and there is

a lack of power calculations to support the representativeness of the study, therefore increasing the likelihood of type 2 error. There is also an element of bias in this type of observational study.

Dula *et al*[6] compared the efficacy of administering intramuscular ketorolac with intramuscular meperidine in the treatment of acute biliary colic. The study consisted of 30 patients who were divided into two groups and after the diagnosis of acute biliary colic was established, were given either meperidine 1.5 mg/kg (100 mg max.) or ketorolac 60 mg. The patients were asked to rate their pain at two time intervals; before administration and 30 min after the medication was given. This was rated on a visual analogue pain scale. The average pain score was compared between the two groups at time 0 and at 30 min. The average pain score at time 0 was 7.6 for the ketorolac group and 7.3 for the meperidine group. The visual analog scale (VAS) scores for the ketorolac group and the meperidine group were 3.8 and 3.9 at the 30-min time interval after the administration of the respective drugs. It was found that there was indeed improvement in pain control in both groups, but there was no markedly demonstrable difference in the pain relief achieved by either ketorolac or meperidine when administered intramuscularly.

This study had a definite aim and was well-designed but the size of the sample was too small to have any impact on the practice. It was a randomized, prospective and a double-blinded study. However there was an absence of power calculations, making the study less representative of the large number of cholelithiasis patients who present to emergency clinics routinely. Only 15 patients effectively got intramuscular ketorolac and this cannot constitute evidence of any consequence.

Henderson *et al*[7] conducted a similar study on 324 patients over a 2-year period with a view to comparing analgesic efficacy and systemic tolerability of intravenous Ketorolac and Meperidine in the treatment of acute biliary colic. The patients were between the ages of 18 and 65 years with signs and symptoms consistent with acute biliary colic. Pain scores were quantified by means of a four-point verbal rating system as well as a VAS. These are validated tools for measuring patient satisfaction and drug efficacy and thus lend validity to the findings. The results did not demonstrate any significant differences in pain or drug tolerability [mean change in the VAS at 2 h was 6.2 ± 3.6 cm for the ketorolac group, compared with 6.7 ± 3.6 cm for the meperidine group (P = 0.25)] but revealed higher incidences of nausea and dizziness in the Meperidine group (n =149). The study goes on to conclude that Ketorolac (n =175) is a well-tolerated and effective analgesia for biliary colic and the fact that it showed similar efficacy as Meperidine with decreased adverse effects makes it a better alternative.

This was a prospective, randomized and a double-blinded study which included a significant sample of patients. The inclusion and exclusion criteria were strictly monitored. The limitation of this study was that out of a sizeable number of patients initially enrolled (n = 534), more than 220 patients were lost for a variety of reasons such as loss of data and inappropriately filled forms. Also the employment of convenience sampling makes the study prone to potential bias. However, the presence of power calculations makes this a robust and acceptable study. There is certainly evidence collected in this study which could potentially change practice; more patients with biliary pathology could be treated with Ketorolac for effective analgesia.

Antevil *et al*[1] undertook a trial to determine the efficacy of intravenous glycopyrrolate for the relief of pain associated with the biliary tract. At the onset 312 patients were assessed for the study but eventually only 39 were actually included in the study. The rest either declined to participate or did not meet the inclusion criteria. The initial aim of the study was to include 54 patients but due to difficulty in patient enrollment, analysis was done on only 39 patients who completed the study protocol. The initial sample size was based on power calculations to give the study a representative character, which was later lost due to the fallouts. The results of the study failed to demonstrate any significant differences in the pain relief between patients receiving glycopyrrolate and those receiving a placebo. The statistical difference in visual analogue scale for pain between the former and the latter was 3 mm *vs* 8 mm respectively. It was proposed that a further, larger study would be needed to underline the supremacy (if any) of glycopyrrolate in treating patients with biliary colic.

This was a randomized, prospective and a double-blind study. The randomization was computer generated and the inclusion criteria were set up keeping in view the final size of the sample based on eligibility criteria. Factors such as the selection of patients and the methods used to sample by the enrolling physicians made the study weaker and the results less relevant. The patients enrolled for the study did not all necessarily have cholelithiasis, thus making them less suitable for treatment with an anti-cholinergic agent like glycopyrrolate. This was highly likely to give false negative results. This study failed to achieve its aim and left a lot to be desired in terms of patient selection and the inclusion criteria.

Kumar *et al*[2] undertook a study to compare the effects of intramuscular diclofenac with intramuscular Hyoscine-N-butyl bromide in the treatment of acute biliary colic and also to study their role in the prevention of gallstone-related complications. The study was conducted on 72 consecutive patients with biliary colic. One group (n = 36) received 75 mg of intramuscular diclofenac and the other group (n = 36) received 20 mg of intramuscular hyoscine. Pain severity was later measured on a visual analog scale at different time intervals of 30 min, 1 h, 2 h, and 4 h after the administration of the drug. Patients were followed for 72 h for signs of relapse or development of complications. It was found that diclofenac provided much

Table 1 Comparison of studies with their design and outcomes

Ref.	Design of study	Sample size	Duration of treatment	Results
Akriviadis *et al*[4]	Randomized controlled trial	*n* = 53 Group Ⅰ (*n* = 26) (NSAID) Group Ⅱ (*n* = 27) (Placebo)	3 d	Superior results from Diclofenac usage
Tomida *et al*[5]	Non-randomized controlled trial	*n* = 527		Ursodeoxycholic acid a safe option in symptomatic but high surgical risk patients
Dula *et al*[6]	Randomized controlled trial	*n* = 30 Group Ⅰ (*n* = 15) (NSAID) Group Ⅱ (*n* = 15) (Meperidine)	1 d	Comparable efficacy but lesser side-effects from Ketorolac
Henderson *et al*[7]	Randomized controlled trial	*n* = 324 Group Ⅰ (*n* = 175) (NSAID) Group Ⅰ (*n* = 149) (Meperidine)		Comparable efficacy but lesser side-effects from Ketorolac
Kumar *et al*[2]	Randomized controlled trial	*n* = 72 Group Ⅰ (*n* = 36) (NSAID) Group Ⅱ (*n* = 36) (Hyoscine)	3 d	Rapid symptom relief with Diclofenac and lower rate of sequelae
Antevil *et al*[1]	Randomized controlled trial	*n* = 39 Group Ⅰ (Glycopyrrolate) Group Ⅱ (Placebo)		No significant difference in analgesia between glycopyrrolate and placebo
Olsen *et al*[9]	Randomized controlled trial	*n* = 46 Group Ⅰ (*n* = 23) (Ketorolac) Group Ⅱ (*n* = 23) (Butorphanol)	1 d	Both agents provided reasonable relief of symptoms
Basurto Oña *et al*[10]	Meta-analysis			NSAIDs drugs of choice for symptom control and improvement of prognosis

NSAIDs: Non-steroidal anti-inflammatory drugs.

more rapid pain relief, as shown by the fact that 91.7% of such patients recorded no symptoms at the 4-h interval. Furthermore, it was noted that progression to sequelae of cholelithiasis was significantly lower in this group of patients compared with the patients treated with hyoscine.

This was a prospective, randomized, and double-blinded study with a significant sample size. There were no dropouts in terms of follow-up and the focus of the study remained unaltered. The results of this study are precise and corroborate well with the past experiences of other researchers like Todd and Sorkin[8] in 1988. The study has, in the authors' opinion, the potential to influence practice if backed by robust statistical analysis.

Olsen *et al*[9] carried out a prospective randomized controlled trial comparing the efficacy of ketorolac *vs* butorphanol for patients with suspected biliary colic in the emergency department. This was a compact study with a definite aim (though limited by a small sample size) which concluded that both agents can be considered reasonable options in patients presenting with biliary colic, especially those with a need for further investigations.

Basurto Oña *et al*[10] conducted a systematic review and meta-analysis of randomized controlled trials involving the management of biliary colic with anti-inflammatory agents. A systematic and manual search was conducted in the literature. The authors selected 7 RCTs of 349 patients. The inclusion criteria were all the RCTs which compared the effects of NSAIDs with other interventions that were employed for treating uncomplicated biliary colic in an acute setting. The outcome measures were set up as rescue analgesia, rapidity of analgesic effect, adverse reactions and progression to complications.

The results were well analyzed and statistically significant. These were expressed in terms of confidence intervals and odds ratios, making the analysis more rigorous. The results showed a clear advantage in favour of NSAIDs because there was lower need for rescue analgesia (OR = 0.32; 95%CI, 0.16-0.61) and progression to complications (OR = 0.19; 95%CI: 0.08-0.44). This is a very robust study and can be assigned as level-I evidence. The results cannot, however, be extrapolated to the general population simply because 349 patients cannot be

representative of a pathology which affects such a large part of the adult population. In these types of studies there is a danger of publication bias in terms of selecting only the favourable trials for the analysis.

The findings of this study are also well supported by observations of Macintyre *et al*[11], who have termed NSAIDs as effective analgesics for the management of acute pain (level- Ⅰ evidence).

DISCUSSION

The review of the above studies clearly suggests that there are no set protocols for the administration of specific analgesic agents to the patients with biliary colic (Table 1). It follows that there is strong evidence demonstrating the therapeutic and preventive potency of NSAIDs in the management of biliary colic, not only in terms of symptom control but in disease progression as well[12]. Apart from studies on diclofenac[4] and ketorolac[2], there are studies[13,14] which have shown that intravenous tenoxicam and injectable flurbiprofen (both NSAIDs) respectively are equally effective in managing biliary colic. The efficacy of NSAIDs has been proven to be superior in comparison to agents such as meperidine and hyoscine. Initial analgesic requirements may be substantial, and treatment with NSAIDs or acetaminophen (also called paracetamol) should be initiated[15]. NSAIDs also demonstrated pharmacological superiority in terms of smaller number of doses and side effects with longer duration of action in comparison to other analgesic agents[4]. Therefore enough qualitative evidence is available to influence practice.

A multi-centric study needs to be undertaken, aimed at identifying the reasons leading to variation in practice between the various centers after these patients are identified as having biliary colic. The evidence provided (level- Ⅰ)[10] is significant and similar studies would go a long way toward laying down strict guidelines for prescribing analgesia to patients with biliary colic.

COMMENTS

Background

Cholelithiasis is a common surgical presentation in developed countries, present in 10% of the adult population and 20% of those aged over 65 years. Biliary colic is a presenting symptom in 75%-80% of those with symptomatic cholelithiasis. Despite this, there are currently no set protocols for the pain management in biliary colic.

Research frontiers

This paper reviews extensive literature from electronic databases including PubMed, Science Direct, Wiley Inter Science, Medline and Cochrane. Six randomized control trials, 1 non-randomized trial and 1 meta-analysis were analysed from the past 15 years.

Innovations and breakthroughs

The aim in this paper was to collate evidence for non-steroidal anti-inflammatory drugs (NSAIDs) use in biliary colic as both pain relief and with a view to preventing further complications.

Applications

This review shows NSAIDs to be both safe and effective for biliary colic pain management as well as reducing the incidence of complications arising from cholelithiasis. Practically this could have implications for increased use of NSAIDs for biliary colic as well as encouraging further study in this area to investigate the role of NSAIDs in improving complication rates.

Peer-review

The article is complete and interesting.

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