Chemopreventive Effect of Nonsteroidal Anti-Inflammatory Drugs on the Development of a New Colorectal Polyp or Adenoma in a High-Risk Population: A Meta-Analysis

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ABSTRACT

Background: Although many experimental, epidemiologic, and clinical studies have suggested that aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in reducing and preventing colorectal adenomas, randomized, controlled trials (RCTs) are still being carried out to obtain statistically reliable results.

Objective: The aim of this meta-analysis was to review long-term, prospective RCTs investigating the effect of NSAIDs on the relative risk (RR) for developing ≥ 1 new colorectal polyp or adenoma in a high-risk population.

Methods: We conducted a comprehensive search of MEDLINE, PubMed, and other electronic databases (including Inter-Science, Science Direct, Ebsco, Synergy, and Proquest) (key terms: *nonsteroidal anti-inflammatory drugs, aspirin, colorectal, and polyps*; years: 1974–2004) for English-language articles. Eligible studies were analyzed in terms of demographic data, adverse effects, and effect of NSAIDs on the RRs.

Results: Four long-term, prospective RCTs were used in the statistical analysis. A total of 2069 high-risk patients were enrolled; 1880 patients completed the studies, and 1127 were in active-treatment groups (aspirin 81–325 mg/d or sulindac 150–300 mg/d). Our meta-analysis of these studies revealed that the overall RR for developing ≥ 1 new colorectal polyp or adenoma was significantly reduced by using aspirin or other NSAIDs (RR = 0.809; 95% CI, 0.718–0.912).

Conclusions: The results of this meta-analysis suggest that regular use of aspirin 81 to 325 mg/d or sulindac 150 to 300 mg/d for ≥ 1 year was associated with a decrease in the RR for developing ≥ 1 new colorectal polyp or adenoma to 0.80 (95% CI, 0.718–0.912) in patients at high risk. (*Curr Ther Res Clin Exp.* 2004;65:345–352) Copyright © 2004 Excerpta Medica, Inc.

Key words: aspirin, colorectal adenoma, colorectal cancer, meta-analysis, NSAIDs, relative risk.

INTRODUCTION

What are the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on colorectal adenomas? Do these drugs prevent or reduce the development of adenomas? Many epidemiologic, animal, and experimental studies of the preventive effects of aspirin or other NSAIDs (eg, sulindac, cyclooxygenase-2 [COX-2] selective inhibitors, indomethacin) on colorectal cancer and adenomas have been performed.¹⁻¹⁰ However, only a few of these studies were prospective, randomized, placebo-controlled clinical trials (RCTs), and although some of the results support the preventive effect of aspirin or other NSAIDs,¹¹⁻¹³ some do not.¹⁴ Thus, it is difficult to make a decision about the net effect of NSAIDs on colorectal adenomas or polyps.

Therefore, the reliability of assessments of the effect of NSAIDs on colorectal adenomas or polyps could be increased by combining the data from similar trials. Meta-analyses of prospective RCTs are of increasing importance, particularly in the field of therapeutic assessment. One meta-analysis of the relationship between NSAID use and colorectal cancer performed in 1994¹⁵ showed that regular aspirin use reduced the risk for colorectal cancer and polyps by ~50%.

The aim of the present meta-analysis was to review long-term, prospective RCTs investigating the effect of NSAIDs on the relative risk (RR) for developing ≥ 1 new colorectal polyp or adenoma in a high-risk population.

MATERIALS AND METHODS

We conducted a comprehensive search of MEDLINE, PubMed, and other electronic databases (including Inter-Science, Science Direct, Ebsco, Synergy, and Proquest) (key terms: *nonsteroidal anti-inflammatory drugs*, *aspirin*, *colorectal*, and *polyps*; years: 1974–2004) for English-language articles on the effects of NSAIDs on the colon and rectum. Forty-five related studies were found. We excluded 22 reviews, 4 experimental studies on prostaglandin levels,⁷⁻¹⁰ 4 observational studies in healthy subjects,¹⁻⁴ 3 studies that lacked information on calculating the RR,¹⁶⁻¹⁸ 2 retrospective studies,^{19,20} 2 animal studies,^{5,6} 1 study related to the factors motivating participation in a colorectal cancer chemoprevention trial,²¹ 1 cost-effectiveness analysis,²² and 2 ongoing studies.^{23,24} After performing homogenization tests, we used 4 studies¹¹⁻¹⁴ containing sufficient data for the calculation of the RR in our meta-analysis.

Statistical Analysis

A fixed-effects model was used for combining the data.²⁵⁻²⁷ Comprehensive Meta-analysis Software version 1.0.23 (Biostat, Inc., Englewood, New Jer-

sey) was used for statistical analyses. $P \leq 0.05$ was considered statistically significant.

RESULTS

All 4 studies had >1 end point, but the RR for developing ≥ 1 new colorectal polyp or adenoma was the only end point common to all 4 studies, and was the mainstay of the present study. The eligibility criteria of the studies and the RRs taken into consideration for these studies are listed in **Table I**.

Patients

The 4 studies in our meta-analysis included 2069 patients at high risk for developing ≥ 1 new colorectal polyp or adenoma, 1880 of whom completed the studies.¹¹⁻¹⁴ The treatment groups comprised 1127 patients; the placebo groups comprised 753 patients. It was calculated that ~ 400 patients would be needed in the treatment and placebo groups to provide a statistically significant decrease in the RR for developing ≥ 1 new colorectal polyp or adenoma. Patients at high risk had an increased risk for developing ≥ 1 new colorectal polyp or adenoma (as evidenced by a history of colorectal cancer and/or the adenomatous polyposis coli gene) compared with healthy subjects. Subjects were excluded from the studies if they had any lesions on the lumen of the colorectum on colonoscopy. In 3 studies,¹¹⁻¹³ which excluded patients with familial adenomatous polyposis, existing polypoidal lesions were removed. In

Table I. Characteristics of eligible patients and relative risks in the studies included in the present meta-analysis.

Study	Eligible Patients	Relative Risks
Baron et al, 2003 ¹¹	≥ 1 Colorectal adenoma removed within 3 months before recruitment, ≥ 1 adenoma removed within 16 months before recruitment, and a history of ≥ 2 adenomas or an adenoma ≥ 1 cm in diameter removed within 16 months before recruitment	New adenoma (any adenoma)
Sandler et al, 2003 ¹²	Histologically documented colon or rectal cancer with a low risk for recurrent disease (ie, patients who underwent curative surgery), good general health with an expected survival of ≥ 5 years	New adenoma (≥ 1 adenomatous polyp)
Benamouzig et al, 2003 ¹³	Histologically confirmed, ≥ 3 adenomas irrespective of size or ≥ 1 adenoma ≥ 6 mm in diameter	New adenoma (recurrence of ≥ 1)
Giardiello et al, 2002 ¹⁴	A disease-causing mutation of the APC gene but with no endoscopically detectable colorectal adenomatous polyps and no history of colonic surgery	New adenoma (≥ 1 adenoma)

APC = adenomatous polyposis coli.

the remaining study,¹⁴ subjects with familial adenomatous polyposis syndrome, but with no history of polypoidal lesions, were included.

The age range for eligibility in all 4 studies was 8 to 80 years. The demographic characteristics of the groups were similar in each study.

Treatments

NSAIDs used in the studies were aspirin^{11–13} (dosage range, 81–325 mg/d) and sulindac¹⁴ (dosage range, 150–300 mg/d). The mean durations of the studies ranged from 12 to 40 months.

Adverse Events

Adverse events (AEs) were graded 1 to 4 (1 = mild, 2 = moderate, 3 = severe, and 4 = life-threatening) according to the Common Toxicity Criteria of the National Cancer Institute (CTCNCI).^{12,14} The most common treatment-related CTCNCI AEs were severe hemorrhage (gastrointestinal, 6 patients [0.8%]; genitourinary, 8 patients [1.6%]) and stroke (7 patients [0.8%]).¹¹ No statistically significant differences in the incidences of AEs were found between the active-treatment and placebo groups in any study.^{11,13,14}

Adenomas

P values and crude RRs for developing ≥ 1 new colorectal polyp or adenoma in the active-treatment and placebo groups in each study are shown in **Table II**. As shown in the table, 2 dosages of aspirin (81 and 325 mg/d) were used in the study by Baron et al,¹¹ and the lower dose was found to have a significant chemopreventive effect. Because no significant difference between the 2 dosages of aspirin was found, the results from those 2 treatment groups were merged for meta-analysis.

According to the homogeneity test result ($Q = 4.08$; $df = 3$; $P = \text{NS}$), these studies could be used for meta-analysis. The results of the meta-analysis and weights of studies are given in **Table III**. The study by Baron et al¹¹ had the highest weight (63.6%), with 1084 subjects, whereas the study by Giardiello et al¹⁴ had the lowest (3.2%), with 41 subjects. Only the study by Sandler et al¹² had a significant RR (RR, 0.612; $P = 0.004$). The other 3 studies^{11,13,14} did not have significant results, although the RR in each study was <1 . These 3 RRs might indicate that NSAID use had a tendency to decrease the RR for developing ≥ 1 new colorectal polyp or adenoma. After combining the RRs of the 4 studies, the overall RR was calculated as 0.809 (95% CI, 0.718–0.912; $P < 0.001$).

DISCUSSION

Animal studies^{5,6} have shown a protective effect of NSAIDs in the colon. NSAIDs inhibit the activity of COX-2, a key enzyme in the pathway of prostaglandin production. Prostaglandins play a key role in the accelerated proliferation of

Table II. Characteristics of the studies included in the present meta-analysis.*

Study/Study Group	Study Duration, Mean	No. of Patients	Age, y	Sex, No. (%)		N/T, No. (%) [†]	Crude RR [‡]
				Males	Females		
Baron et al, 2003 ¹¹	3 y	1121	–	712 (63.5)	409 (36.5)	–	–
Aspirin 81 mg/d	–	372	57.4 (9.9) [§]	233 (62.6)	139 (37.4)	160/355 (45.1)	0.957
Aspirin 325 mg/d	–	381	57.3 (9.9) [§]	244 (64.0)	137 (36.0)	140/366 (38.3)	0.812
Placebo	–	368	57.7 (9.1) [§]	235 (63.9)	133 (36.1)	171/363 (47.1)	–
Sandler et al, 2003 ¹²	31 mo	635	39–70	332 (52.3)	303 (47.7)	–	–
Aspirin 325 mg/d	–	317	–	164 (51.7)	153 (48.3)	43/259 (16.6)	0.612
Placebo	–	318	–	168 (52.8)	150 (47.2)	70/258 (27.1)	–
Benamouzig et al, 2003 ¹³	1 y	272	–	190 (69.9)	82 (30.1)	–	–
Aspirin 160/300 mg/d	–	140	57.8 (1.5) [‡]	98 (70.0)	42 (30.0)	38/126 (30.2)	0.73
Placebo	–	132	57.7 (1.7) [‡]	92 (69.7)	40 (30.3)	46/112 (41.1)	–
Giardiello et al, 2002 ¹⁴	≥40 mo	41	–	14 (34.1)	27 (65.9)	–	–
Sulindac 150/300 mg/d	–	21	12.9 (5.1) [‡]	5 (23.8)	16 (76.2)	9/21 (42.9)	0.779
Placebo	–	20	15.8 (8.7) [‡]	9 (45.0)	11 (55.0)	11/20 (55.0)	–

N/T = no. of patients with a new adenoma among total patients at the end of the study; RR = relative risk for developing ≥ 1 new colorectal polyp or adenoma.

*Adverse events were nonsignificant^{11,12,14} or data were unavailable¹³ (control vs treatment).

[†]Patients who underwent a follow-up endoscopy ≥ 1 year after randomization were included in the analyses.

[‡]Univariate or unadjusted RRs for developing ≥ 1 new colorectal polyp or adenoma.

[§]Mean (SD).

^{||} $P = 0.016$ versus placebo.

[¶] $P = 0.004$ versus placebo.

Table III. Results of the meta-analysis.*

Study	Treated	Control	RR	95% CI	N	ES	W%†	P	0.5	1.0	2.0
Baron et al, 2003 ¹¹	300/721	171/363	0.883	0.769–1.015	1084	–0.124	63.6	0.085			
Sandler et al, 2003 ¹²	43/259	70/258	0.612	0.448–0.876	517	–0.491	19.6	0.004			
Benamouzig et al, 2003 ¹³	38/126	46/112	0.730	0.519–1.038	238	–0.308	13.6	0.080			
Giardiello et al, 2002 ¹⁴	9/21	11/20	0.779	0.414–1.468	41	–0.249	3.2	0.437			
Overall	391/1127	298/753	0.809	0.718–0.912	1880	–0.195	100.0	0.001			

RR = relative risk for developing ≥ 1 new colorectal polyp or adenoma; N = no. of patients at study end; ES = effect size.

*Homogeneity test result: $Q = 4.08$; $df = 3$; $P < 0.253$.

†Weights of the studies in the meta-analysis.

tumor tissue.⁹ In addition, increasing evidence shows that NSAIDs might induce cell-cycle arrest and apoptosis in colorectal tumor cells.^{7–10}

Observational trials^{2–4} investigating the chemopreventive effect of NSAIDs for colorectal adenomas in healthy subjects have conflicting results. In 1 observational study² of only male physicians, no effect was observed with aspirin 325 mg QD (RR, 1.03; 95% CI, 0.83–1.28). In another study,³ regular use (≥ 2 times/wk) of aspirin by male health care professionals significantly reduced the total RR for colorectal cancer (RR, 0.68; 95% CI, 0.52–0.92). In a third observational study⁴ of healthy women who consistently received ≥ 2 aspirin tablets per week, no significant reduction in the RR for colorectal cancer was found compared with nonusers after 4 years (RR, 1.06; 95% CI, 0.78–1.45). Although these studies were comprehensive, they would not be appropriate for the current meta-analysis because they included different populations (healthy subjects), and were not placebo controlled. Considering the results of the present study, NSAIDs are more efficacious in patients with a high risk for developing ≥ 1 new colorectal polyp or adenoma than in the healthy subjects.

In 2 retrospective studies,^{19,20} odds ratios (ORs) were estimated at ~ 0.5 . Regular use of NSAIDs was associated with a 50% reduction in the RR for developing ≥ 1 new colorectal polyp or adenoma compared with occasional NSAID use or nonuse. In the present meta-analysis, retrospective studies were not used. If the incidence of ≥ 1 new adenoma is more common in high-risk patients using an NSAID than in healthy people, then the OR would lead to a considerable overestimation of the RR.²⁴

In a meta-analysis¹⁵ of the relationship between NSAID use and colorectal cancer, it was reported that “in all but one of seven recent epidemiological case-control and cohort studies directly examining the association between aspirin and colorectal cancer and polyps, regular aspirin use reduced the risk of these diseases by about half.” Because that meta-analysis included different types of studies (eg, case-control and cohort studies), it might have had some biases inherent to the study designs.^{28,29} In the present meta-analysis, however,

only prospective RCTs and only high-risk patients were included to enhance the integrity of the results and to avoid potential biases.²⁷

CONCLUSIONS

The results of this meta-analysis suggest that regular use of aspirin 81 to 325 mg/d or sulindac 150 to 300 mg/d for ≥ 1 year was associated with a decrease in the RR for developing ≥ 1 new colorectal polyp or adenoma to 0.809 (95% CI, 0.718–0.912) in patients at high risk.

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