ORIGINAL ARTICLE

Comparison of rectal indomethacin with co-administration of rectal indomethacin and sublingual nitroglycerin on prevention of post ERCP pancreatitis: A double blinded randomized controlled trial

Seyed Saeid Sarkeshikian[1], Maryam Jameshorani[2], Ahmad Hormati[3*], Mohammad Reza Ghadir[4], Mahdi Pezeshki[5], Mohammad Aghaali[6]

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BACKGROUND: Acute pancreatitis is the most common complication developing after endoscopic retrograde cholangiopancreatography (ERCP). Most recent studies have reported preventive effects of rectal indomethacin (RI) and sublingual nitroglycerin (SN) on post-ERCP pancreatitis (PEP). However, superiority of their co-administration to indomethacin alone has not been proven. This study assessed effects of the co-administration of RI and SN on preventing PEP.

METHOD: Being a double-blind randomized controlled trial, this study was performed on 392 patients who had undergone ERCP. They were assigned to two groups. Group 1 (n=196) received 100 mg RI and 0.4 mg SN before and after ERCP, respectively. Group 2 (n=196) received 100 mg RI and sublingual placebo before and after ERCP, respectively. All the patients were examined after 24 hours in terms of signs and symptoms of pancreatitis and the serum amylase level.

RESULTS: Of all the patients, 21 (6.5%) developed pancreatitis (10 [5.1%] in Group 1 and 11 [5.6%] in Group 2) (p=0.82). The relative risk reduction, absolute risk reduction, and number needed to treat were respectively 9.1%, 0.5%, and 196 patients.

CONCLUSION: As compared with the single administration of RI, the co-administration of RI (before ERCP) and SN (after ERCP) does not reduce the incidence of PEP. Multicenter trials are recommended for confirming these findings.

Key Words: *ERCP; Pancreatitis; Rectal indomethacin; Sublingual nitroglycerin.*

Abbvreviations: CBD: Common Bile Duct; ERCP: Endoscopic Retrograde Cholangiopancreatograph; Nsaids: Nonsteroidal Anti-Inflammatory Drugs; PEP: Post-ERCP Pancreatitis; RI: Rectal Indomethacin; SD: Standard Deviation; SN: Sublingual Nitroglycerin; SOD: Sphincter of Oddi Dysfunction

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a medical technique in which a side view endoscope is introduced to the second part of duodenum and radio contrast material is injected in to the pancreatic and biliary tract through the Trans the scope catheters. This invasive procedure is used to explore pancreatic and biliary tract disorders and is regarded as the most sensitive technique for diagnosing obstructive jaundice. ERCP is also used as a treatment procedure for sphincterotomy, choledocholithiasis extraction, and obtaining biopsy (1), just As other endoscopic procedures, it is associated with some complications, Of them, pancreatitis is considered to be the most common (2,3). In different studies, its incidence varies from 1% to 40% (4-7). Post-ERCP pancreatitis (PEP) is a clinical syndrome characterized by a worsening of abdominal pain or the onset of abdominal pain with an increase in the amylase and lipase levels over three times the normal limit 24 hours after ERCP, which requires more than an overnight hospitalization (8). The intensity of PEP varies and, based on the patient's stay in the hospital, is divided into three types, namely mild (a 3-day stay), moderate (a 3- to 10-day stay), and severe (a stay for more than 10 days) (1). Risk factors involved in the development of PEP are categorized into two groups, namely patient- and technique-related ones. Patient-related risk factors include sphincter of Oddi dysfunction (SOD), young age, female gender, normal values of bilirubinemia, and a history of previous pancreatitis. Technique-related risk factors include difficult cannulation, the balloon dilatation of the biliary sphincter, and the injection of contrast into the pancreatic duct (9-11). Various studies have suggested many mechanisms for the induction of PEP. For example, inadvertent catheterization of pancreatic duct may cause its injury which is aggravated after coming into contact with contrast and intestinal contents and, finally, an inflammatory process occurs. Moreover, due to an excessive injection of contrast into the duct, increased hydrostatic pressure can initiates an inflammatory process, thereby activating pancreatic enzyme secretion (12). A large number of studies have been conducted investigating how to avoid the risk of this complication, such as use other diagnostic methods instead ERCP, do it by experienced endoscopist, placement of prophylactic pancreatic stents, minimization of the number of cannulation and volume of contrast injections into the pancreatic duct (13) According to them, it is likely to disrupt the process resulting in pancreatitis by inhibiting part of the inflammatory pathway (14,15). The consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) has been recommended for this purpose. By interrupting the inflammatory cascade, they can reduce PEP significantly (15-17). The first clinical trial performed in 2003 explored effects of rectal indomethacin (RI) on preventing PEP, which considerably reduced the incidence rate by 6.4% in the target group and by 15.5% in the control group (18). Further relevant studies have confirmed these results (19-21). Several studies and meta-analyses have reported that nitroglycerin (as an effective drug in preventing sphincter of Oddi spasm), in addition to NSAIDs, can reduce pancreatitis significantly. They have indicated that nitroglycerin in sublingual form is more effective than other routs of administration (22,23). Significantly, most studies have Shown the beneficial role of NSAIDs alone (10). Nevertheless, the effect of dual therapy has not been assessed sufficiently. The present study aimed to assess role of co-administering sublingual nitroglycerin (SN) and RI in preventing PEP. In the current study, RI alone was administered to one group and SN and RI were co-administered to the other group. The objective was to compare the rate of pancreatitis and drug side effects in two groups.

[1]Assistant Professor of Gastroenterology, Gastroenterology and Hepatology Disease Research Center, Qom University of Medical Sciences, Qom, [2]Assistant Professor of Internal Medicine, Metabolic Disease Research Center, Zanjan University of Medical Sciences, Zanjan, Iran; [3]Assistant Professor of Gastroenterology, Gastroenterology and Hepatology Disease Research Center, Qom University of Medical Sciences, Qom, [4]Gastroenterologist, Gastroenterology and Hepatology Disease Research Center, Qom University of Medical Sciences, Qom, Iran; [5]General Practitioner, Gastroenterology and Hepatology Disease Research Center, Qom University of Medical Sciences, Qom, Iran; [6]Department of Epidemiology, School of Public Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Correspondence: Dr. Ahmad Hormati, Assistant Professor of Gastroenterology, Gastroenterology and Hepatology Disease Research Center, Qom University of Medical Sciences, Qom, Iran, Telephone: +989125534323,, Fax: +982536122053, e-mail: hormatia@yahoo.com

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METHODS

The present study was a Double-blind randomized controlled trial. It was carried out on patients who had attended the Gastroenterology clinics of Shahid Beheshti Hospital in Qom in 2016 and were candidates for diagnostic and therapeutic ERCP. The sampling method was convenience sampling and the subjects were randomly assigned to the groups (Figure 1).

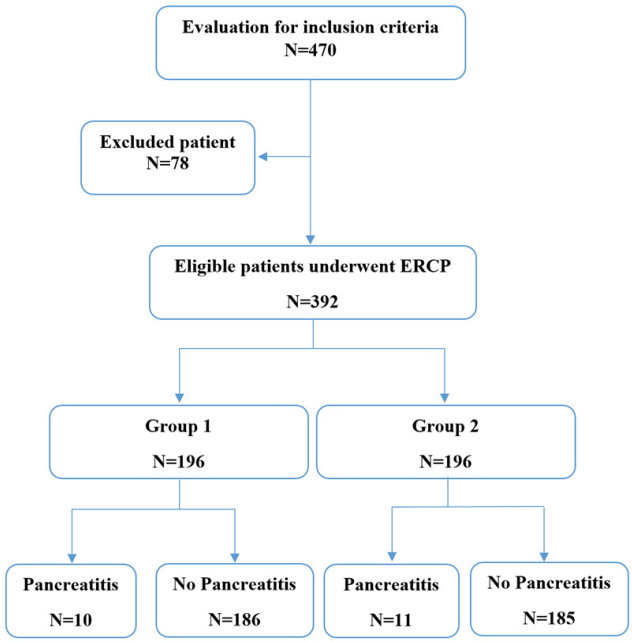

Figure 1) *Patient flow diagram of rectal indomethacin with sublingual nitroglycerin (Group 1) vs. rectal indomethacin and sublingual placebo (Group 2) for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis.*

An independent researcher carried out the block randomization for the 2 groups with block sizes of four. Sample size was estimated using a specific clinical trial formula. The inclusion criteria were as follows: 1) Age between 18 and 70 the 18-70, 2) the presence of ERCP indications, particularly pancreatic-biliary diseases, bile leakage, biliary tract stenosis after surgery and CBD stones; 3) the palliative treatment of malignancies inducing biliary obstruction. The exclusion criteria were contraindications to use nitroglycerin (severe anemia, angle-closure glaucoma, increased intracranial pressure, severe allergy to nitrates, and orthostatic hypotension) and indomethacin (allergy to aspirin and NSAIDs, history of peptic ulcers complication, history of gastrointestinal bleeding). Out of 470 patients, 392 meeting the criteria underwent ERCP (Figure 1). In both group there were not factors that influence the risk of PEP such as use of pancreatotoxic drugs. Shortly before ERCP, the two groups of the patients were given indomethacin suppositories (100 mg). Right after the process, the intervention group (Group 1) received SN and the control group (Group 2) received sublingual placebos. In order to avoid the impact of personal opinions on the interpretation of the results, the drugs were coded (blindness was maintained). The only person who was aware of the codes was the one in charge of administering the drugs to the patients. Unaware of the coding, the examiner investigated pancreatitis in the patients. After the process, the onset of abdominal pain or a worsening of former abdominal pain with an increase in the pancreatic enzyme levels over three times the normal limit 24 hours after ERCP was regarded as PEP. The patients with the following conditions were considered to be at high risk of developing PEP: Sphincter of oddi dysfunction (SOD), the Inadvertent canulation of pancreatic duct, balloon dilatation of the ampulla of Vater, and, at least, one of the following: female gender, age <60, no dilatation of the common bile duct (CBD) (<8 mm in patients with history of cholecystectomy and <6 mm in patients without such history) normal serum bilirubin level (total serum bilirubin level <1), and failure to clean the bile duct and/or maintain the biliary flow. A physician using a three-part questionnaire including pre-ERCP data, data acquired during ERCP, and post-ERCP data collected the patients' data. In the Descriptive Statistics section, the mean and standard deviation (SD) were used for quantitative variables but frequency indices were used for qualitative variables. Using the chi-square test or Fisher's exact test, the qualitative variables of the two groups were compared. The quantitative variables of the groups were compared using the independent t-test. In order to counterbalance effects of confounding variables, logistic regression was applied. The data were analyzed using the SPSS program, version 22. This study has been registered in the Iranian Registry of Clinical Trials (ID: IRCT20161205031252N5). The Safety Monitoring and Human Studies Review Board in Shahid Beheshti Hospital approved protocol of the study. The Board provided regulatory oversight by reviewing the research protocol and blinded subject data quarterly. All the participants provided written informed consent. Any case of PEP, other complications of the procedure, and adverse events that were potentially attributable to the intervention was reported to the local Institutional Review Board and the Data and Safety Monitoring Board. It must be mentioned that the present study has attempted to adhere to CONSORT guidelines.

RESULTS

There was no difference between the two groups in the demographic variables (Table 1).

TABLE 1

Demographic variables in the two groups

Variables		Group 1 (%)	Group 2 (%)	P
Gender	Female	116 (59.2)	110 (56.1)	0.61
	Male	80 (40.8)	86 (43.9)	
Initial ERCP indications	CBD stone	143 (73)	139 (71)	0.68
	Suspected SOD	12 (6.1)	14 (7.1)	
	Pancreatobiliary tumors	28 (14.3)	34 (17.3)	
	Others	13 (6.6)	14 (4.6)	
History of pancreatitis		13 (6.6)	9 (7.1)	0.51
History of cholecystectomy		36 (18.4)	37 (18.9)	0.9
Comorbidity		70 (35.7)	64 (32.6)	0.59
		SD	SD	
Age		60.64 (± 19.31)	63.92 (± 17.23)	0.07
BMI (Body Mass Index)		26.73 (± 3.74)	26.48 (± 3.61)	0.5

In regard to paraclinical findings, the two groups were identical except in frequency of CBD stenosis (p=0.02) (Table 2).

TABLE 2

A comparison between the two groups in terms of para-clinical findings

Variables	Group 1 Mean ± SD	Group 2 Mean ± SD	P
AST	106.27 ± 131.23	100.74 ± 110.78	0.65
ALT	117.36 ± 131.15	124.27 ± 136.19	0.61
ALP	551.15 ± 449.07	625.47 ± 497.13	0.12
Total bilirubin	4.20 ± 5.78	4.94 ± 6.34	0.22
Direct bilirubin	2.79 ± 3.95	3.42 ± 4.25	0.13
CBD diameter in ERCP	14.33 ± 6.19	14.19 ± 5.33	0.81
CBD stenosis in ERCP	41 (20.9%)	63 (32.1%)	0.02

As a confounding variable, it was included in the multivariate analyses. There was no significant difference between the two groups with respect to procedures applied during ECP, including the frequency of pancreatic canulation (p=0.75), stent placemen (p=0.051), and the type of sphincterotomy (p=0.073). The only significant difference between the two groups was in the administered drugs during ERCP i.e., glucagon and hyoscine (p=0.004). As a confounding variable, it was included in the multivariate analyses. Results of the chi-square test demonstrated that there was no significant difference between the two groups with respect to the success rate of maintaining the CBD flow (p=0.06); however, considering a p-value<0.1, this was identified as a potential confounding variable. According to results of the independent t-test, there was no significant difference between the two groups with respect to the post-ERCP amylase level (p=0.07). Except the frequency of periampullary diverticula, there was no significant difference between the two groups with respect to the risk factors for PEP (Table 3).

TABLE 3

Risk factors for PEP in the two groups

		Group 1 (%)	Group 2 (%)	P
The risk factors	Suspected SOD	12 (6.1)	14 (7.1)	0.84
	Female	115 (58.7)	110 (56.1)	0.68
	Age < 60	86 (43.9)	74 (37.8)	0.26
Normal bilirubin		65 (33.2)	60 (30.6)	0.66
Normal CBD diameter		17 (8.7)	23 (11.7)	0.4
papillary balloon dilatation		44 (22.4)	41 (20.9)	0.81
Failure to clean the duct		15 (7.7)	18 (9.2)	0.72
Cannulation of the pancreatic duct > 1		45 (23)	47 (24)	0.91
Pancreatic duct stenting		30 (15.3)	28 (14.3)	0.89
Diverticula		50 (25.5)	34 (17.3)	0.05
High-risk population		136 (69.4)	132 (67.3)	0.75
Number of risk factors		2.05 (1.17)	2.02 (1.25)	0.81

This was identified as a potential confounding variable. There was no significant relationship between the demographic variables and the incidence of PEP (Table 4). There was no significant relationship between the incidence of PEP and the paraclinical findings (Table 4).

TABLE 4

A comparison between the incidence frequency of PEP, demographic variables and the paraclinical findings

Pancreatitis Incidence Demographic variables		PEP (21), N (%)	No PEP (371), N (%)	P-value
Gender	Female	14 (66.7)	174 (46.9)	0.55
	Male	7 (33.3)	129 (34.8)	
Initial ERCP indications	CBD stone	16 (76.2)	218 (58.8)	0.65
	Suspected SOD	1 (4.8)	20 (5.4)	
	Pancreatobiliary tumors	4 (19)	46 (12.4)	
	Others	0 (0)	19 (5.1)	
History of pancreatitis		2 (9.5)	20 (5.4)	0.75
History of cholecystectomy		4 (19)	56 (15.1)	0.86
Comorbidity		8 (38.1)	104 (28)	0.46
		Mean (SD)	Mean (SD)	
Age		63.9 (16.09)	61.8 (18.73)	0.62
BMI (Body Mass Index)		26.41 (3.42)	26.75 (4.56)	0.74
AST		144.38 ± 152.56	101.29 ± 120.93	0.12
ALT		151.09 ± 133.05	117.94 ± 132.95	0.27
ALP		611.14 ± 506.22	578.39 ± 467.46	0.76
Total bilirubin		5.71 ± 6.93	4.41 ± 6.00	0.34
Direct bilirubin		3.98 ± 5.58	2.98 ± 3.96	0.27
CBD diameter in ERCP		17.93 ± 13.07	14.03 ± 14.94	0.24
CBD stenosis in ERCP		4 (19%)	78 (21%)	0.83

Furthermore, investigating the association of the frequency of PEP with procedures performed during ERCP revealed that there was a significant relationship between CBD stenting and the incidence of PEP, as 6.7% of the PEP cases were associated with CBD stenting (p = 0.003); however, there was no significant association between PEP and the other ERCP variables including the type of sphincterotomy (p=0.53), drugs used during ERCP (p=0.69) and cannulation frequency (p=0.35). Based on the results of the chi-square test, there was no significant association between the success in maintaining the CBD flow and the incidence of PEP (p=0.24) (Figure 2). Considering the results of the independent t-test, there was a significant relationship between the incidence of PEP and the amylase level (p=0.002) so that the patients with pancreatitis had a higher amylase level (a mean of 1032 versus 113). The risk factors for pancreatitis were compared with the incidence frequency of PEP and no significant relationship was observed between them. PEP was developed in 21 patients at all (5.4%).

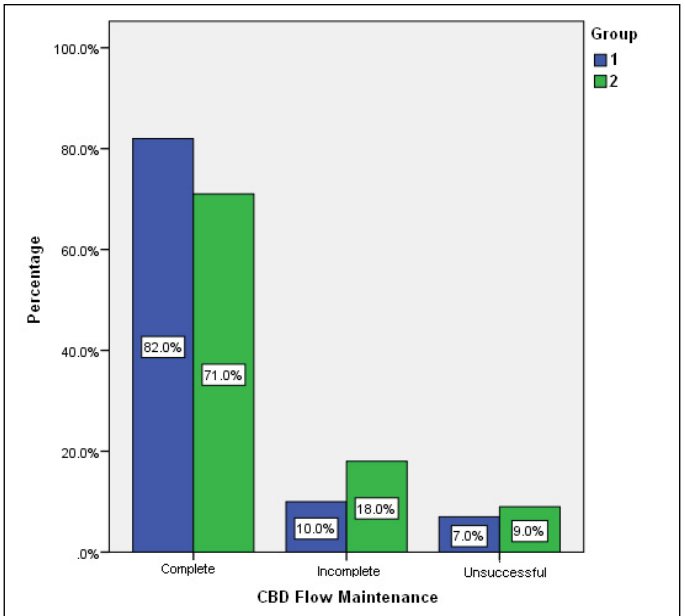

Figure 2) *A comparison between the incidence frequency of PEP and the success in maintaining the CBD flow*

Of them, 10 (5.1%) and 11 (5.6%) were in groups 1 (case) and 2 (control), respectively. (Risk ratio [RR] = 0.91, 95% CI: 0.4-2.09). There was no statistically significant association between the treatment group and PEP (p=0.82, relative risk reduction [RRR] = 9.1%, 95% CI: -109.14-60.48; absolute risk reduction [ARR] = 0.5%, 95% CI: -3.9-4.9; number needed to treat [NNT] = 196, 95% CI: 20- (-25)). There was no statistically significant difference with respect to the drug-related adverse effects among the treatment groups (Table 5).

TABLE 5

The frequency of PEP in the two groups

		PEP	
		Yes	No
Group	Rectal indomethacin with sublingual nitroglycerin	10 (5.1%)	186 (94.9%)
	Rectal indomethacin and placebo	11 (5.6%)	185 (94.4%)
	Total	21 (5.4%)	371 (94.6%)

DISCUSSION

In this study we found that the strategy of prophylactic pre-ERCP administration of rectal indomethacin in all patients appears similar to the strategy of rectal indomethacin plus Sublingual Nitroglycerin, also according to the results, although the incidence of pancreatitis in the first (case) group was lower than that in the second (control) group, the difference is not statically significant. There was no statistically significant relationship between the treatment group and PEP. After removing the confounding variables (such as periampullary diverticula, CBD stenosis, prescribed medication and success in drainage, which were significantly different in the two groups and counterbalancing their effect using multivariate analysis,it was found that there was no statistically significant association between the intervention group and pancreatitis (p=0.98). Thus, it could be mentioned that, although the risk of the disease in the first group (case) was 0.91, as compared with control group, and the intervention seemed to have a

protective role, the co-administration effects of RI and SN on preventing PEP was not statistically different from effects of the single administration of RI. Moreover, after multivariate tests were conducted, periampullary diverticula (p = 0.03, OR = 3.54, 95% CI: 1.11-11.31) was identified as the independent risk factors for PEP. This association might be related to difficult canulation and less canulation success rate usually occurs in patients with periampullary diverticula (32,33) Various studies have determined effects of nitroglycerin and NSAIDs, as compared with placebos, on preventing PEP (15-28). Nevertheless, there are very few studies which have compared these two drugs or have compared their co-administration effects with effects of each one in isolation. In the only study which has compared effects of nitroglycerin and NSAIDs on the prevention of PEP, Bhatia et al. found no significant difference between 380 patients with respect to the incidence of clinical pancreatitis (29). In the only similar study carried out by Sotoudehmanesh et al. with the aim of comparing the co-administration of RI and SN with the single administration of RI, it was demonstrated that the incidence of PEP was significantly reduced after the co-administration (28). However, in the present study, although the co-administration reduced the incidence of PEP, this reduction was not statistically significant. In two meta-analyses, it has been shown that preventive effects of nitroglycerin on groups with a high incidence of PEP have been more significant (14,29); thus, one of the reasons for the difference could have been the difference in the total incidence of PEP in the groups (11.1% versus 5.3% in the study by Sotoudehmanesh et al. and the present study, respectively). The other differences between the current study and the study by Sotoudehmanesh et al. were the following: a lower incidence of PEP in the two groups (5.1% versus 6.7% in those who received nitrates and indomethacin and 5.6% versus 15.3% in the indomethacin group, respectively, in the present study and the study by Sotoudehmanesh et al.) and the difference in the time point of drug administration so that the drugs were administered to the patients after ERCP in the present study while they were done before ERCP in the study by Sotoudehmanesh et al. As for the incidence rate of PEP in the RI group, the results of the present study were in line with results of the study by Elmunzer et al. in which indomethacin was administered after ERCP and the rate was 9.2% (30). In a study on 602 high-risk patients, Elmunzer et al. showed that, as compared with the placebo, RI (100 mg) reduced the incidence of PEP. Another difference between the present study and the study by Sotoudehmanesh et al. was the frequency of pancreatic duct stenting in the two groups in the studies (15.3% versus 5.3 in the group of nitrates and indomethacin and 14.3% versus 6% in the indomethacin group in the present study and the study by Sotoudehmanesh et al., respectively). Since pancreatic duct stenting has been used as a standard preventive treatment of PEP for a long time and has been recommended in available guidelines for preventing pancreatitis in high-risk patients (3,30,31), a lower incidence of PEP in the present study could have been related to this to some extent. In the current study, the frequency of high-risk patients was 68.4% (as compared with 82.7% in the study by Sotoudehmanesh et al.). The difference in the number of patients with a high risk of PEP could justify the difference in the incidence of PEP in the two studies. Although the study by Elmunzer et al. yielded results similar to those in the current study, all the patients had been selected among high-risk patients. In summary, as compared with the single administration of RI, the co-administration of RI (before ERCP) and SN (after ERCP) did not reduce the incidence of PEP. Multicenter trials are required to confirm these findings.

CONCLUSION

The current study explored the effect of co-administration of RI and SN on preventing PEP. According to the results of the study, the co-administration of RI (before ERCP) and SN (after ERCP), compared with the single administration of RI, did not reduce the incidence of PEP. Not excluding those with a history of sphincterotomy from the present study could be one of its limitations since it is said that selective CBD cannulation in patients with a history of previous sphincterotomy is performed easily and the risk of PEP in these patients is lower (29). Another limitation in the current study was that it was a single-center one. By conducting multicenter research trials with a larger sample size, removing potential confounding variables, and considering PEP risk factors, better results will be achieved.

DECLARATIONS

Ethics approval and consent to participate

All individuals signed a written consent form. The study was approved by the Research Ethics Committee at Qom University of Medical Sciences (Code: IR.MUQ.REC.1394.133).

Consent for publication

All the authors give consent for publication.

Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available due to protection of participant confidentiality but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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