Oral N-Acetyl cysteine versus rectal indomethacin for prevention of post ERCP pancreatitis: a multicenter multinational randomized controlled trial

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ABSTRACT – Background – This multicenter multinational RCT designed to compare the efficacy of suppository indomethacin and NAC for prevention of PEP. Methods – During a 6-month period, all of the ERCP cases in seven referral centers were randomly assigned to receive either 1200 mg oral NAC, indomethacin suppository 100 mg, 1200 mg oral NAC plus indomethacin suppository 100 mg or placebo 2 hours before ERCP. The primary outcomes were the rate and severity of any PEP. Results – A total of 432 patients included (41.4% male). They were originally citizens of 6 countries (60.87% Caucasian). They were randomly allocated to receive either NAC (group A, 84 cases), rectal indomethacin (group B, 138 cases), NAC + rectal indomethacin (group C, 115 cases) or placebo (group D, 95 cases). The rate of PEP in groups A, B and C in comparison with placebo were 17.4%, 7.8% vs 20% (P=0.08, 0.614 & 0.01 respectively). The NNT for NAC, indomethacin and NAC + indomethacin was 11, 38 and 8 respectively. Conclusion – Oral NAC is more effective than rectal indomethacin when compared to placebo for prevention of PEP and the combination of NAC and Indomethacin had the lowest incidence of PEP and may have synergistic effect in preventing of PEP (IRCT20201222049798N1; 29/12/2020). Keywords – Post ERCP pancreatitis; NAC; rectal indomethacin.

INTRODUCTION

Nowadays, endoscopic retrograde cholangiopancreatography (ERCP) as an endoscopic procedure is performed mostly due to its therapeutic options and capabilities and like other medical procedures, has both minor and major complications. The most common major complication of ERCP is pancreatitis, with a prevalence of 2.1% to 24.4% and average 5%-8%. Post ERCP pancreatitis (PEP) is diagnosed following an increase in serum amylase above three times the normal level more than 24 hours after ERCP, along with new computed tomography scan (CT) findings or new-onset abdominal pain that are compatible with pancreatitis, which may require hospitalization or extending the duration of hospital stay of patients who were hospitalized in the first place6,7). PEP still has unclear pathophysiology. It can be resulted from combined injury from papillary manipulation and trauma with instruments such as cannulation resulting in edema or spasm of the sphincter of Oddi or contrast overloading inside the pancreatic duct with resultant hydrostatic damage8,9,10. Other possible mechanisms are chemical, microbiologic, thermal and or enzymatic although the relative role of each is unclear11-13.

Different medications and interventions have been used to prevent this complication or attenuate its severity, but are of little benefit11-13. Beside active hydration and Non-steroidal anti-inflammatory drugs (NSAIDs) suppository, other noteworthy medications include octreotide, somatostatin, gabexate mesylate, corticosteroids,
heparin and allopurinol. In this regard, one of the hypothesis involves the role of active oxygen species and oxidative stress in the pathogenesis of pancreatitis by activation of inflammatory cascade and immune responses. Based on this theory, N-acetyl cysteine (NAC) as an anti-oxidant agent inhibits inflammatory intermediates and oxidative stress and potentially could prevent pancreatitis. Despite unsuccessful experiments with the intravenous form of this drug, a Randomized Controlled Trial (RCT) as pilot study in 2013 found that oral NAC could be effective for prevention of PEP. Based on results of this study and according to the low price, safety profile, and negligible adverse effects of this drug, the current study as a multicenter multinational Randomized Controlled Trial was designed to evaluate efficacy of oral NAC in comparison with rectal indomethacin and placebo for prevention of PEP.

METHODS

During a 6-month period, from September 2020 to February 2021, all of the patients who met standard indications for ERCP in seven referral centers of four countries and had no contraindications for participating in the study were included. Exclusion criteria included the presence of uncontrolled diabetes mellitus, admission due to established pancreatitis before ERCP, unwillingness to undergo ERCP, serum Triglyceride >1000 mg/mL, and anatomical changes to the stomach from previous surgeries.

Before enrolling to the study, a description of the study protocol and potential hazards were given to all patients according to the Declaration of Helsinki and all of the participants were requested to sign an informed consent and then they were randomly assigned to four groups to receive either 1200 mg oral NAC in 150 cc water (group A), indomethacin suppository 100 mg (group B), 1200 mg oral NAC in 150 cc water plus indomethacin suppository 100 mg (group C) or 150 cc water as placebo (group D) 2 hour before ERCP. Randomization was performed by computer and random numbers chain (each center 80 cases). The primary outcomes were the rate and severity of any PEP among participants. The study was approved by Ethical Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.HGOLESTAN.REC.1399.120) and registered in the Iran Clinical Trial Registration site as IRCT2020122049798N1; 29-12-2020.

An algorithm was designed for this RCT (FIGURE 1). Before performing ERCP, baseline serum amylase and lipase levels were obtained from all patients. Patients took either the medication or placebo 2 h before ERCP. At 24 h after ERCP, patients’ serum amylase and lipase levels were measured. Additionally, patients were examined for abdominal pain compatible with acute pancreatitis (AP) by experienced gastroenterologists. The duration of the hospital stay after procedure was also recorded. Almost all of the ERCP procedures were performed by gastroenterologists. Before or during procedure, the operators did not use any other preventiv procedur or medications such as aggressive hydration or pancreatic stent. At the end of the study period, the recorded data was retained for final analysis.

The normal upper limits of amylase and lipase defined as <65 to 85 U/mL based on reference kit of each center. Pancreatitis defined as serum amylase levels >275 U/mL or serum lipase levels 3 times more than upper normal limit with the presence of abdominal pain and/or compatible imaging findings. The severity of pancreatitis is defined based on the number of hospitalized days following ERCP as mild (<4 days), moderate (4 to 10 days), or severe (>10 days).

RESULTS

Overall, a total of 432 patients were included (average age 57.3 y, range 16 to 99, 41.4% male) during the study period. The demographic characters of participants are mentioned in TABLE 1. The participants were originally citizens of six countries and about 60.87% of the study population were of Caucasian descent (TABLE 2). The most common indication for ERCP was Cholelithiasis (66.89%) (TABLE 3). The patients were randomly allocated to receive either NAC (group A, 84 case), rectal indomethacin (group B, 138 cases), NAC + rectal indomethacin (group C, 115 cases) or placebo (group D, 95 cases). The rate of bleeding and perforation after procedures was 3.94% and 2.54% respectively.
The rate of PEP in groups A (NAC), B (indomethacin) and C (NAC + indomethacin) in comparison with D (placebo) were 10.7% (9 cases), 17.4% (24 cases), 7.8% (9 cases) vs 20% (19 cases) ($P=0.08$, 0.614 & 0.01 respectively). The number need to treat (NNT) for NAC, indomethacin and NAC + indomethacin were 11, 38 and 8 respectively. 49.18% of the PEP cases were mild with average duration of hospital stay 4.5 days (range 1 to 14 days) and no sever PEP happened in groups A and C (TABLE 4). The rate of abdominal pain after ERCP in groups A, B, C in comparison with D (placebo) were 28.6% (24 cases), 33.3% (46 cases), 19.1% (22 cases) vs. 27.4% (26 cases) ($P=0.85$, 0.33 & 0.15 respectively). Average duration of hospital stay after ERCP in groups A, B, C in comparison with D were 3.6 days, 2.6 days, 2.8 days vs. 3.7 days ($P=0.396$, 0.010 & 0.012 respectively).

In head to head comparison, the efficacy of NAC, rectal indomethacin and combination of NAC + rectal indomethacin for prevention of PEP were 46.5%, 13% and 61% more than placebo respectively and NAC and NAC + rectal indomethacin were 38.5% and 55.2% more effective than rectal indomethacin.

**DISCUSSION**

Pancreatitis is the most common serious ERCP complication which depend on several factors[1,3,31-33]. Some of these factors are patient specific (eg. age, sex), while the others are related to the procedure itself or endoscopist experience[34]. Several agents have been proposed for the pharmacologic prophylaxis of PEP, mostly directed toward amelioration of the inflammatory cascade that accompanies and potentiates AP[27]. Accordingly, one of the supposed agents with controversial results is NAC due to its anti-oxidant and anti-inflammatory properties[28]. While most of the frustrated experiences with this medicine had applied to its intravenous form such as Katsinelos et al. study in 2005[30], or combination of oral and intravenous form by Milewski et al. in 2006[29], a pilot study by Alavinejad et al. in 2013 revealed promising results for prevention of PEP[31]. The results of this study showed a reduction in the rate of PEP in the treated group compared with the placebo group (10% vs 28%, $P=0.02$) and they concluded oral NAC could be useful for prevention of PEP and explained the different results because of differences in the mode of NAC prescription as oral solution or intravenous formula. The limitation of this study is that it was a pilot one and performed as a single center.

So the current study was designed as multicenter multinational RCT to evaluate not only efficacy of oral NAC but also to compare its usefulness with rectal indomethacin as one of the most widely used medications for this indication[16,34,35]. Based on our findings the rate of PEP among those who received NAC or combination of NAC + rectal indomethacin were 10.7% and 7.8% in comparison with 20% in placebo group ($P=0.08$ & 0.01 respectively) and 17.4% in those who just received rectal indomethacin ($P=0.175$ & 0.024 respectively). So the combination of NAC + rectal indomethacin significantly reduced the rate of PEP and even NAC per se was able to decrease PEP although it was statistically non meaningful ($P=0.08$). NNT of NAC and NAC + rectal indomethacin were 11 and 8 respectively.

On the other hand, the average duration of hospital stay after ERCP among those who managed with NAC + rectal indomethacin was almost 1 day shorter (2.8 days vs 3.7 days) and according of average charges for each day more stay in hospital (from 4000 to 5000$) this combination could be cost effective. The probable explanation for the mechanism of action of NAC could be reduction of concentration of NF-kB in pancreatic ducts which was supposed by a study from Sweden[37]. They found that NAC suppressed monocyctic NF-kB activation induced by AP and suggested

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**TABLE 1. Demographic characters of participants.**

<table>
<thead>
<tr>
<th>Group</th>
<th>A (NAC)</th>
<th>B (rectal indomethacin)</th>
<th>C (NAC + rectal indomethacin)</th>
<th>D (Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M /F ratio</td>
<td>35/49</td>
<td>53/85</td>
<td>53/62</td>
<td>40/55</td>
</tr>
<tr>
<td>Average age (range), y</td>
<td>57–98</td>
<td>55–99</td>
<td>56–111</td>
<td>61–53</td>
</tr>
<tr>
<td>CBD stone*</td>
<td>59</td>
<td>105</td>
<td>88</td>
<td>66</td>
</tr>
<tr>
<td>N, %</td>
<td>(70.2%)</td>
<td>(76%)</td>
<td>(76.5%)</td>
<td>(76.3%)</td>
</tr>
</tbody>
</table>


**TABLE 2. Ethnic background of participants.**

<table>
<thead>
<tr>
<th>Ethnicities</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>43</td>
<td>96</td>
<td>66</td>
<td>58</td>
<td>263</td>
</tr>
<tr>
<td>Asian</td>
<td>22</td>
<td>14</td>
<td>27</td>
<td>24</td>
<td>87</td>
</tr>
<tr>
<td>Arab</td>
<td>10</td>
<td>14</td>
<td>16</td>
<td>6</td>
<td>46</td>
</tr>
<tr>
<td>African</td>
<td>4</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Indian</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Turk</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
<td>138</td>
<td>115</td>
<td>95</td>
<td>432</td>
</tr>
</tbody>
</table>

**TABLE 3. Indications for ERCP.**

<table>
<thead>
<tr>
<th>Indications</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute cholangitis</td>
<td>16</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3.70%</td>
</tr>
<tr>
<td>Ampullary Cancer</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.85%</td>
</tr>
<tr>
<td>Biliary obstruction</td>
<td>58</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13.42%</td>
</tr>
<tr>
<td>Biliary colic</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0.23%</td>
</tr>
<tr>
<td>Biliary leak</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>0.92%</td>
</tr>
<tr>
<td>CBD Dilatation</td>
<td>17</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3.93%</td>
</tr>
<tr>
<td>CBD Stone</td>
<td>289</td>
<td>66</td>
<td>66</td>
<td>66</td>
<td>66.89%</td>
</tr>
<tr>
<td>CBD Stricture</td>
<td>14</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3.24%</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.85%</td>
</tr>
<tr>
<td>Choledochal cyst</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0.23%</td>
</tr>
<tr>
<td>Icterus</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0.23%</td>
</tr>
<tr>
<td>Malignant obstructive jaundice</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.46%</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2.31%</td>
</tr>
<tr>
<td>PSC</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.69%</td>
</tr>
<tr>
<td>Total</td>
<td>432</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

ERCP: endoscopic retrograde cholangiopancreatography; CBD: common bile duct; PSC: primary sclerosing cholangitis.

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**TABLE 4. Relative prevalence of PEP in study groups based on severity.**

<table>
<thead>
<tr>
<th>Severity</th>
<th>A (NAC)</th>
<th>B (rectal indomethacin)</th>
<th>C (NAC + rectal indomethacin)</th>
<th>D (Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild PEP</td>
<td>2 (22.2%)</td>
<td>15 (62.5%)</td>
<td>3 (33.3%)</td>
<td>10 (52.6%)</td>
</tr>
<tr>
<td>Moderate PEP</td>
<td>7 (77.7%)</td>
<td>6 (25%)</td>
<td>6 (66.6%)</td>
<td>7 (36.8%)</td>
</tr>
<tr>
<td>Severe PEP</td>
<td>0 (0%)</td>
<td>3 (12.5%)</td>
<td>0 (0%)</td>
<td>2 (10.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>24</td>
<td>9</td>
<td>19</td>
</tr>
</tbody>
</table>

PEP: post ERCP pancreatitis; ERCP: endoscopic retrograde cholangiopancreatography.
a potential therapeutic approach by restoration of the functional capacity of the immune system in AP. The mentioned NAC as an NF-κB inhibitor, preferentially reaching the local inflammatory foci, could be a potential future way of intervention. The role of NF-κB activity in induction of inflammatory cascade and primary stages of AP and its amelioration by NAC treatment has been confirmed by Axelsson et al. study(39).

These results prove NAC and specially its combination with rectal indomethacin as an effective and practical option for preventing PEP. Premedication with rectal indomethacin (group B) resulted in 24 cases with PEP (17.4%) which was similar to placebo (P=0.614) and in contrast with a systemic review and meta-analysis by Shen et al. in 2017(40). Another systemic review by Imamdar et al. in 2017 found controversial results and reported rectal indomethacin to be protective against PEP in just high-risk patients versus placebo but not protective in average-risk patients(41). Our findings about rectal indomethacin are in concordance with a RCT by Levenick et al. in 2016 and another meta-analysis by Dubravcisk et al. that conclude rectal indomethacin did not prevent post-ERCP pancreatitis(30,42). Despite these controversial results about the preventive role of rectal indomethacin(43), some authors have doubts about it and desire its use to be made mandatory before ERCP(42).

The advantages of this RCT were to be a Multicenter Multinational one and participation of considerable number of cases (432 participants) with different racial descents (TABLE 2). Although our study had a limitation and as it performed during COVID-19 pandemic, some of the centers were unable to fulfill pertained number of cases because of social restrictions and decrease in number of procedures per scheduled time(43).

CONCLUSION

In conclusion, oral NAC is more effective than rectal indomethacin when compared to placebo for prevention of PEP and the combination of NAC and Indomethacin had the lowest incidence of PEP and may have a synergistic effect in prevention of PEP. This combination could also be cost effective by reducing the average of PEP and may have a synergistic effect in prevention of PEP. This combination of NAC and Indomethacin had the lowest incidence of PEP when compared to placebo for prevention of PEP and the number of procedures per scheduled time(44,45).

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RESUMO – Contexto – Este estudo randomizado, controlado multicêntrico e multinacional foi projetado para comparar a eficácia da indometacina suppositorio e N-acetil cisteína (NAC) para prevenção de pancreatite pós colangiografia endoscópica. Métodos – Durante um período de 6 meses, todos os pacientes submetidos à CPRE em sete centros de referência foram aleatoriamente atribuídos para receber 1200 mg de NAC oral, supositório de indometacina 100 mg, 1200 mg de NAC oral mais supositório de indometacina 100 mg ou placebo 2 horas antes do procedimento. Os resultados primários foram a taxa e a gravidade de qualquer pancreatite pós procedimento (PPP). Resultados – Um total de 432 pacientes foram incluídos (41,4% do sexo masculino). Eram originalmente cidadãos de seis países (60,87% caucassianos). Foram alocados aleatoriamente para receber NAC (grupo A, 84 casos), indometacina retal (grupo B, 138 casos), NAC + indometacina retal (grupo C, 115 casos) ou placebo (grupo D, 95 casos). A taxa de PPP nos grupos A, B e C em comparação com o placebo foi de 10,7%, 17,4%, 7,8% vs 20% (P=0,08, 0,614 e 0,01, respectivamente). Conclusão – A NAC oral é mais eficaz do que a indometacina retal quando comparado ao placebo para prevenção de PPP e a combinação de NAC e indometacina teve a menor incidência de PPP e pode ter efeito sinérgico na sua prevenção de PPP. (IRCT20201222049798N1; 29/12/2020).

Palavras-chave – Pancreatite pós-CPRE; NAC; indometacina retal.
REFERENCES