JOURNAL

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ORIGINAL ARTICLE: Clinical Endoscopy

Lactated Ringer's solution in combination with rectal indomethacin for prevention of post-ERCP pancreatitis and readmission: a prospective randomized, double-blinded, placebo-controlled trial CME

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ABOUT THE ARTICLE

- **Title:** Lactated Ringer's solution in combination with rectal indomethacin for prevention of post-ERCP pancreatitis and readmission: a prospective randomized, double-blinded, placebo-controlled trial
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- **Institute:** Cooper Medical School of Rowan University
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BACKGROUND

- Acute pancreatitis is a feared adverse event (AE) of ERCP
- The incidence of post-ERCP pancreatitis (PEP) ranges widely in the literature
  - 1 -10% for low-risk individuals
  - 25 -30% for individuals with **high-risk factors**

    such as pancreatic sphincterotomy, sphincter of Oddi dysfunction,

    and history of PEP

  To reduce the risk of PEP, several authors have advocated for the prophylactic placement of a pancreatic duct (PD) stent.

BACKGROUND

- One such agent is **rectal indomethacin (IND)** that acts by

  inhibiting cyclooxygenase and phospholipase A2, compounds believed to have pivotal roles in the pathogenesis of acute pancreatitis.

- The use of an infusion of **lactated Ringer's solution (LR)** has shown a benefit in the prevention of acute pancreatitis.

  attenuating tissue acidification -> prevent zymogen activation, maintain a stable pancreatic microcirculation

BACKGROUND

- This study aim to evaluate the use of **IND with LR**
- when compare with placebo to prevent PEP in high-risk patient

METHOD

STUDY DESIGN

- Patients were enrolled at a tertiary care center in USA
- This study was in compliance with the Declaration of Helsinki and approved by the investigational review board
- The trial was registered online at clinicaltrial.gov before enrollment of any patients

PATIENTS

- Those undergoing ERCP and deemed high risk for PEP by standard criteria

Major criteria (1 of the following)

- Suspicion for sphincter of Oddi dysfunction
- Personal history of PEP
- More than 8 cannulation attempts
- Precut sphincterotomy
- Endoscopic papillary balloon dilation of an intact sphincter
- Endoscopic PD sphincterotomy
- Ampullectomy

Minor criteria (≥2)

- Female and age <50
- Personal history of recurrent acute pancreatitis
- PD injection leading to “acinarization”
- Over 3 PD injections
- PD cytology acquisition

PATIENTS

Exclusion criteria

- **Age<18**
- **Pregnancy**
- **Active acute pancreatitis**
- **NSAID-related exclusionary criteria** : Allergy to NSAIDs, Use of NSAIDs the day of the procedure, Acute renal failure (Cr>1.2), active PU
- **Contraindications to aggressive IVF hydration** : Clinical volume overload(peripheral or pulmonary edema), Respiratory compromise(O2 sat<90 RA), CKD (CrCL<40), systolic CHF (EF<45%), cirrhosis, severe electrolyte disturbance with Na<130 or >150
- **Patients who not meet high risk criteria**

PATIENTS

- Initial demographic data were obtained including

  - Age, Sex, Race, Medical history, prior ERCP data, and AEs if present.

- All patients underwent laboratory data including

  - Basic metabolic panel, amylase levels, and lipase levels before their ERCP

INTERVENTION

- Informed consent
- Computerized random patients **1:1:1:1 ratio** -> 4 treatment groups
    - NSS + rectal placebo
    - NSS + rectal IND
    - LR + rectal placebo
    - LR + rectal IND
- Kept the data in institution’s central pharmacy
- Blind the endoscopist and the patients

INTERVENTION

- Opaque brown plastic bag over each liter of IVF administered -> complete infusion within 30 minutes
- Rectal IND and placebo were obtained from the same compounding pharmacy (Delran Pharmacy)
- ERCP – performed by 1 of 2 fellowship-trained, experienced (>200 cases a year)therapeutic endoscopists.

OUTCOMES

Primary outcome : PEP

PEP defined by the presence of 2/3

1. New or worsening abdominal pain consistent with acute pancreatitis
2. Pancreatic enzymes elevation ≥ 3 times the upper limit of normal 24 hour after the procedure
3. resultant or prolongation of existing hospitalization ≥ 2 nights

OUTCOMES

Secondary outcomes :

- Severe acute pancreatitis (persistent organ failure ≥ 48 hr)
- Localized AEs (pseudocyst, abscess, walled of necrosis)
- Death
- Length of hospital stay in days
- Readmission within 30 days
- AEs related to the study drugs

    - NSAIDs : Anaphylaxis, GI bleeding, ARF

    - IVF : Peripheral/Pulmonary edema, hypoxia, CHF, ascite

OUTCOMES

Monitor outcomes

- Pain severity assessment (10-point Likert scale)
  - Before ERCP, 2 hr, 24 hr, 30 days after ERCP
- Collection of a serum amylase and lipase at least once in a 24-hour period
- Telephone call within 24 hour and also at 30 days from their procedure to ask about delayed AEs
- All data were recorded by blinded study staff -> Triple blinding

RESULTS

PATIENTS

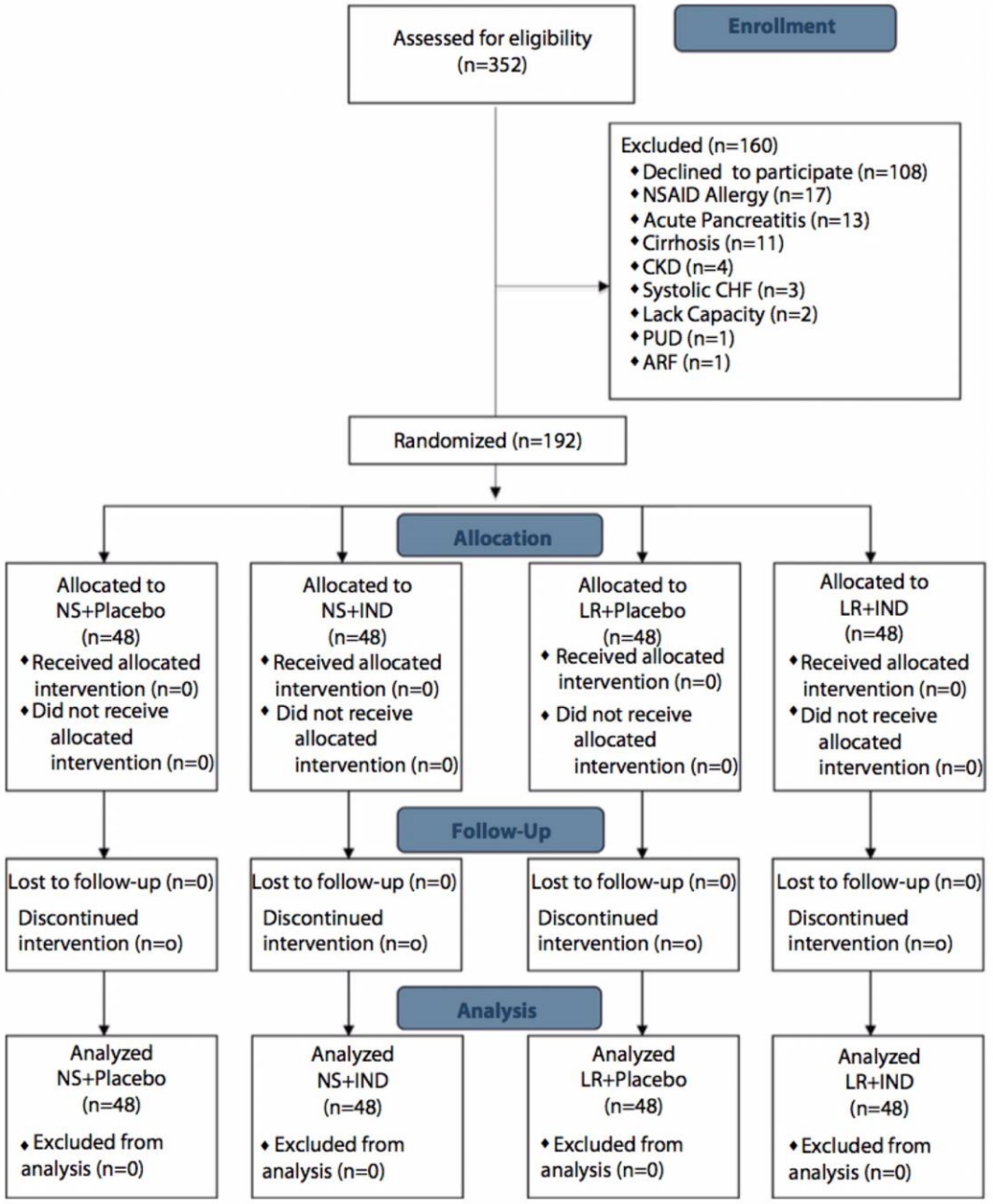


Figure 1. Flow diagram with enrollment and outcomes. *NSAID*, nonsteroidal anti-inflammatory drug; *CKD*, chronic kidney disease; *CHF*, congestive heart failure; *PUD*, peptic ulcer disease; *ARF*, acute renal failure; *NS*, normal saline solution; *IND*, indomethacin; *LR*, lactated Ringer's solution.

TABLE 1. Baseline patient characteristics

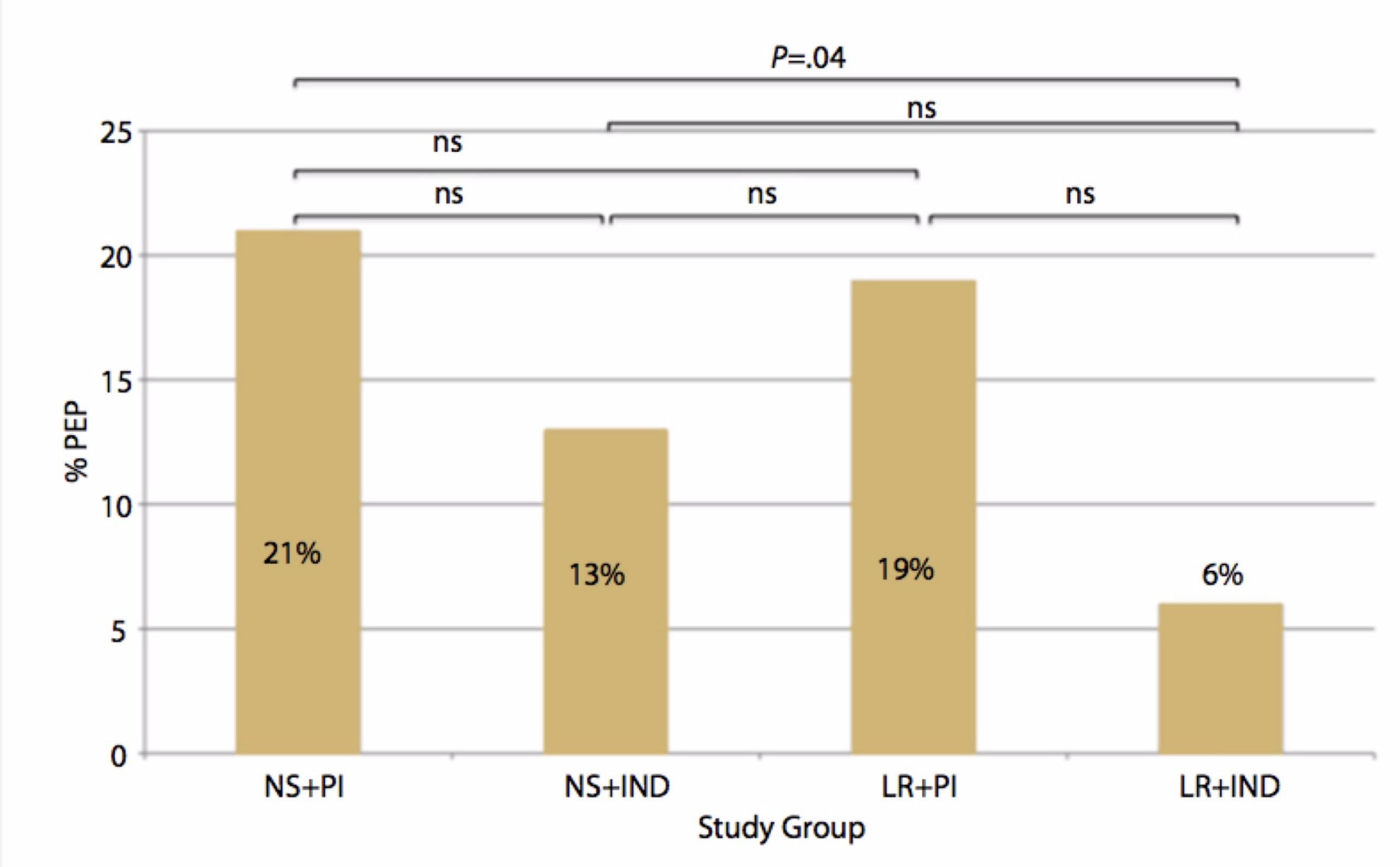
	NS + placebo (n = 48)	NS + IND (n = 48)	LR + placebo (n = 48)	LR + IND (n = 48)	*P* value
Mean age, y	58	62	58	63	.44
Sex					
Female	29 (60%)	33 (69%)	35 (73%)	23 (48%)	.06
Male	19 (40%)	15 (31%)	13 (27%)	25 (52%)	
Race					
White	32 (67%)	35 (73%)	40 (83%)	40 (83%)	.56
African American	3 (6%)	3 (6%)	3 (6%)	4 (8%)	
Hispanic	10 (21%)	8 (17%)	4 (8%)	3 (6%)	
Asian	2 (4%)	2 (4%)	1 (2%)	1 (2%)	
Other	1 (2%)	0	0	0	
Clinical suspicion of SOD					
Any	8 (17%)	8 (17%)	11 (23%)	6 (13%)	.31
Type 1	2 (4%)	4 (8%)	2 (4%)	1 (2%)	.63
Type 2	6 (13%)	4 (8%)	8 (17%)	5 (9%)	.69
Type 3*	0	0	1 (2%)	0	1.00
SOD manometry	3 (6%)	0	2 (4%)	0	.17
Mean risk score (number)†	2	1.9	2.2	1.5	.83
Female and age < 50	11 (23%)	10 (21%)	16 (33%)	5 (11%)	.06
Normal total bilirubin (<1 mg/dL)	27 (56%)	33 (69%)	25 (52%)	23 (48%)	.30
History of PEP	3 (6%)	1 (2%)	3 (6%)	0	.32
History of recurrent pancreatitis	10 (21%)	7 (15%)	11 (23%)	10 (21%)	.78
Difficult cannulation (>8 attempts)	6 (13%)	8 (17%)	5 (10%)	6 (13%)	.87
Biliary sphincterotomy	38 (79%)	40 (83%)	41 (85%)	36 (75%)	.62
Balloon dilation of an intact sphincter	10 (21%)	9 (19%)	11 (23%)	10 (21%)	.74
Precut sphincterotomy	1 (2%)	0	1 (2%)	0	1.00
Plastic biliary stent	8 (17%)	5 (10%)	10 (21%)	11 (23%)	.38
SEMS	7 (15%)	6 (13%)	3 (6%)	3 (6%)	.62
Pancreatography	15 (31%)	12 (25%)	15 (31%)	10 (21%)	.59
Pancreatic sphincterotomy	5 (10%)	4 (8%)	6 (13%)	2 (4%)	.59
Minor duct papillotomy	3 (6%)	3 (6%)	4 (8%)	1 (2%)	.69
>3 Injections of the PD + 1 to the tail	9 (19%)	5 (10%)	9 (19%)	6 (13%)	.58
Pancreatic acinarization	6 (13%)	5 (10%)	7 (15%)	7 (15%)	.96
PD cytology	1 (2%)	2 (4%)	1 (2%)	0	1.00
PD stent placement	15 (31%)	12 (25%)	15 (31%)	10 (21%)	.59
Ampullectomy	2 (4%)	1 (2%)	0	1 (2%)	.90
Trainee involvement	48 (100%)	48 (100%)	48 (100%)	48 (100%)	1.00

PRIMARY OUTCOME

TABLE 2. Primary and secondary study outcomes

	NS + placebo (n = 48)	NS + IND (n = 48)	LR + placebo (n = 48)	LR + IND (n = 48)	*P* value
PEP	10 (21%)	6 (13%)	9 (19%)	3 (6%)	*
Severe PEP	0	1 (2%)	0	0	1.00
Pseudocyst	0	0	0	1 (2%)	1.00
Pulmonary edema	1 (2%)	0	0	0	1.00
Renal failure	1 (2%)	1 (2%)	1 (2%)	1 (2%)	1.00
GI bleeding	0	0	0	0	1.00
Anaphylaxis	0	0	0	0	1.00
Death	1 (2%)	2 (4%)	2 (4%)	1 (2%)	1.00
Readmission	6 (13%)	2 (4%)	2 (4%)	1 (2%)	*
Mean length of stay, days	2.3	2.2	1.9	4.3	.50

PRIMARY OUTCOME [%PEP]

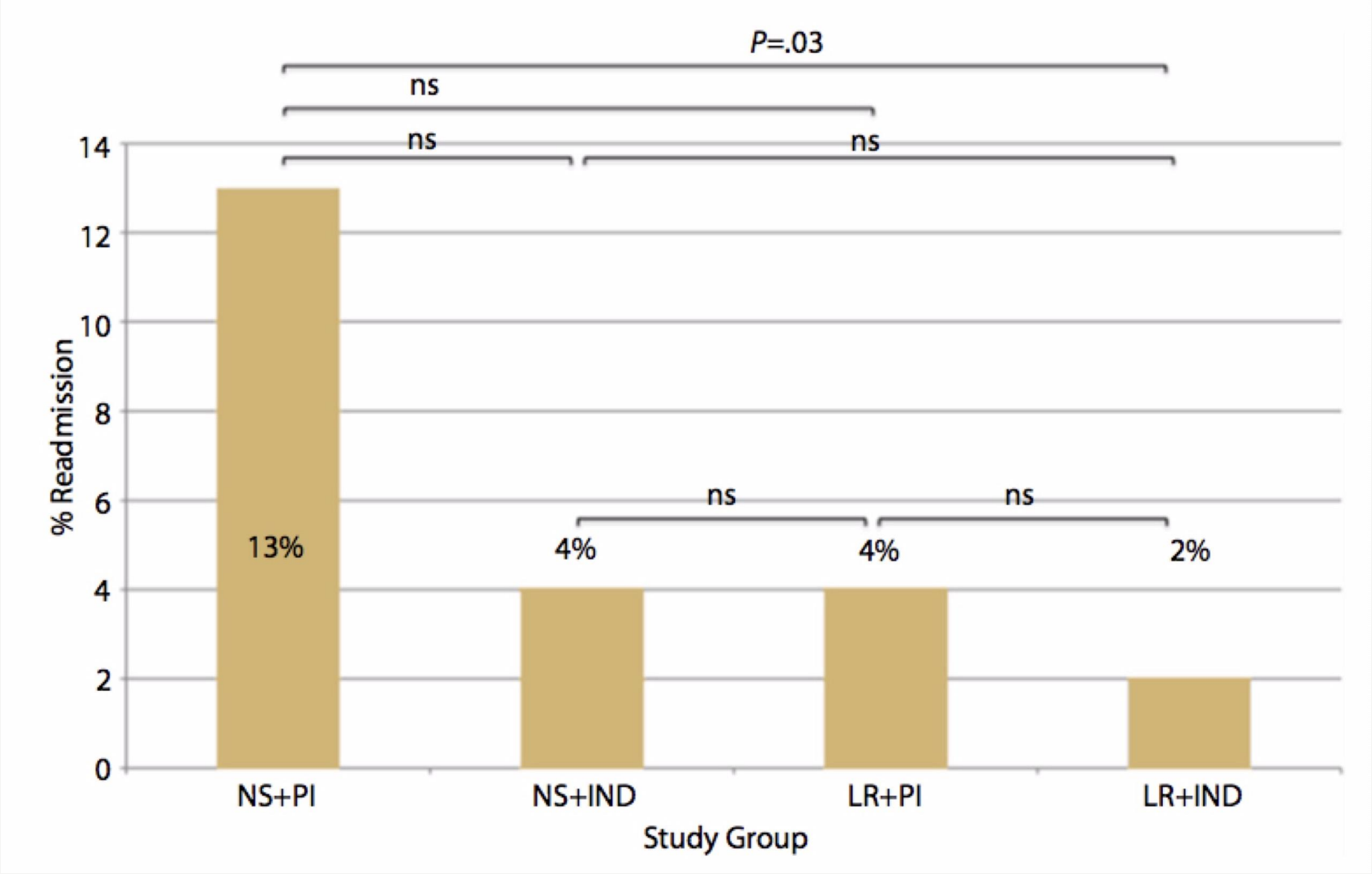


SECONDARY OUTCOMES

TABLE 2. Primary and secondary study outcomes

	NS + placebo (n = 48)	NS + IND (n = 48)	LR + placebo (n = 48)	LR + IND (n = 48)	*P* value
PEP	10 (21%)	6 (13%)	9 (19%)	3 (6%)	*
Severe PEP	0	1 (2%)	0	0	1.00
Pseudocyst	0	0	0	1 (2%)	1.00
Pulmonary edema	1 (2%)	0	0	0	1.00
Renal failure	1 (2%)	1 (2%)	1 (2%)	1 (2%)	1.00
GI bleeding	0	0	0	0	1.00
Anaphylaxis	0	0	0	0	1.00
Death	1 (2%)	2 (4%)	2 (4%)	1 (2%)	1.00
Readmission	6 (13%)	2 (4%)	2 (4%)	1 (2%)	*
Mean length of stay, days	2.3	2.2	1.9	4.3	.50

SECONDARY OUTCOMES [%READMISSION]



ADVERSE EVENTS

- **Total 5 AEs occurred (3%)**
  - 4 ARFs (1 patient in each group)-
  - 1 Pulmonary edema in NSS+Placebo

DISCUSSION

- **Lower incidence of PEP in patients who received combination therapy with LR+ IND compared with NSS+Placebo**
- **Lower readmission rates between LR+ IND compared with NSS+Placebo**
- **NNT 6.9** to prevent 1 episode of PEP

- IND alone reduced PEP (13%) compared with placebo (21%) ,not statistically significant -> presumably because of the small sample size

DISCUSSION

- And our statistical power was not generated for this particular comparison -> Difficult to generate conclusion from this finding

- LR + placebo group (LR alone) – no difference in the rates of PEP as compared with NS+placebo (19% VS 20%)

DISCUSSION

- Strength of this study included
  - Rigorous inclusion criteria for high-risk patients
  - 100% capture of follow-up data
  - Triple blinding strategy
- Limitations
  - Sample size
  - Single-center

THANK YOU