**Supplementary Online Content**

eMethods. Search protocol

eFigure 1. Risk of Bias of Included Studies, RoB 2 Excel Marco Form Manual (Beta Version 7)

eTable 2. GRADE Working Group grades of evidence (GradePro GDT)

**E methods: *SEARCH PROTOCOL***

A comprehensive search of several databases from each database's inception to August 2022, English language, was conducted. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for Liposomal Bupivacaine for Hemorrhoidectomy. The actual strategy listing all search terms used and how they are combined is available in the appendix.

**EMBASE** <1974 to 2022 August 19>

1 exp bupivacaine/ or (Anekain or Bicain or Bipuvacaine or Bucaine or Bupicaina or Bupinex or Bupirop or Bupisen or Bupivan or Bupivacain\* or Bupizenge or Buvacaina or Buvasin or Carbostesin or Chirocaina or Dolanaest or Eladur or Exparel or Inibsa or Kamacaine or Levobupivacaine or Macaine or Marcain or Marcaina or Marcaine or Optesia or Picain or Posidur or Posimir or Senpivac or Sensocaine or Sensorcaine or Sensoricaine or Xaracoll).mp. 46041

2 exp liposome/ or liposom\*.mp. 104376

3 anal canal/su or rectum/su or hemorrhoid/su or anus fissure/su or hemorrhoidectomy.mp. or anoplasty.mp. or ((anorectal or anus or anal or rectal or rectum) adj4 (surgery or surgical or procedure\* or operation\*)).mp. 33153

4 1 and 2 and 3 = 43

**MEDLINE OVID**

1 exp Bupivacaine/ or (Anekain or Bicain or Bipuvacaine or Bucaine or Bupicaina or Bupinex or Bupirop or Bupisen or Bupivan or Bupivacain\* or Bupizenge or Buvacaina or Buvasin or Carbostesin or Chirocaina or Dolanaest or Eladur or Exparel or Inibsa or Kamacaine or Levobupivacaine or Macaine or Marcain or Marcaina or Marcaine or Optesia or Picain or Posidur or Posimir or Senpivac or Sensocaine or Sensorcaine or Sensoricaine or Xaracoll).mp. 18517

2 exp Liposomes/ or liposom\*.mp. 74573

3 anal canal/su or rectum/su or hemorrhoids/su or Fissure in Ano/su or hemorrhoidectomy.mp. or anoplasty.mp. or ((anorectal or anus or anal or rectal or rectum) adj4 (surgery or surgical or procedure\* or operation\*)).mp. 30096

4 1 and 2 and 3 = 17

**Cochrane**

Cochrane Central Register of Controlled Trials

Issue 7 of 12, July 2022 = 25 results

Cochrane Database of Systematic Reviews

Issue 8 of 12, August 2022 = 1 result

#1 [mh Bupivacaine] or (Anekain or Bicain or Bipuvacaine or Bucaine or Bupicaina or Bupinex or Bupirop or Bupisen or Bupivan or Bupivacain\* or Bupizenge or Buvacaina or Buvasin or Carbostesin or Chirocaina or Dolanaest or Eladur or Exparel or Inibsa or Kamacaine or Levobupivacaine or Macaine or Marcain or Marcaina or Marcaine or Optesia or Picain or Posidur or Posimir or Senpivac or Sensocaine or Sensorcaine or Sensoricaine or Xaracoll):ti,ab,kw 15757

#2 [mh Liposomes] or liposom\*:ti,ab,kw 3535

#3 [mh ^"anal canal"/SU] or [mh ^rectum/SU] or [mh ^hemorrhoids/SU] or [mh ^"Fissure in Ano"/SU] or (hemorrhoidectomy or anoplasty):ti,ab,kw or ((anorectal or anus or anal or rectal or rectum) NEAR/4 (surgery or surgical or procedure\* or operation\*)):ti,ab,kw 4873

#4 #1 AND #2 AND #3 = 26

**Web of Science - searched Science Citation Index (SCI), Conference Proceedings Citation Index (CPCI) and BIOSIS Citation Index (BCI)**

#1 TS=(Anekain or Bicain or Bipuvacaine or Bucaine or Bupicaina or Bupinex or Bupirop or Bupisen or Bupivan or Bupivacain\* or Bupizenge or Buvacaina or Buvasin or Carbostesin or Chirocaina or Dolanaest or Eladur or Exparel or Inibsa or Kamacaine or Levobupivacaine or Macaine or Marcain or Marcaina or Marcaine or Optesia or Picain or Posidur or Posimir or Senpivac or Sensocaine or Sensorcaine or Sensoricaine or Xaracoll)

#2 liposom\* (Topic)

#3 (anorectal or anus or anal or rectal or rectum or hemorroid\* or "fissure in ano" or "anus fissure") NEAR/4 (surgery or surgical or procedure\* or operation\*) (Topic) or hemorrhoidectomy or anoplasty (Topic)

#4 #1 AND #2 AND #3

[48 results from Core Collection, and 4 results from BCI]

**eFigure 1. Risk of Bias of Included Studies, RoB 2 Excel Marco Form Manual (Beta Version 7)**



eTable 2. GRADE Working Group grades of evidence (GradePro GDT)

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Liposomal Bupivacaine** | **conventional anesthetic or Placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| **Vomiting - Adverse effects (assessed with Presence/absence of symptoms or signs)** | | | | | | | | | | | | |
| 2 | randomized trials | not serious | seriousa | not serious | very seriousa | strong association dose-response gradient | 2/119 (1.7%) | 7/119 (5.9%) | **OR 2.72** (0.00 to 1973.83) | **86 more per 1,000** (from -- to 933 more) | ⨁⨁⨁◯ Moderate | IMPORTANT |
| **Pain during bowel movements (assessed with Presence/absence of symptoms or signs)** | | | | | | | | | | | | |
| 2 | randomized trials | not serious | seriousb | not serious | very seriousb | strong association dose-response gradient | 2/119 (1.7%) | 6/119 (5.0%) | **OR 2.60** (1.31 to 5.16) | **71 more per 1,000** (from 15 more to 165 more) | ⨁⨁⨁◯ Moderate | IMPORTANT |
| **Pain Scores (assessed with a Validated 10-point numeric rating scale)** | | | | | | | | | | | | |
| 2 | randomized trials | serious | not serious | not serious | not serious | strong association dose-response gradient |  | | | | ⨁⨁⨁⨁ High |  |
| **Time to the first opioid** | | | | | | | | | | | | |
| 3 | randomized trials | seriousc | not serious | not serious | not serious | strong association dose-response gradient |  | | | | ⨁⨁⨁⨁ High |  |
| **Dose of Opioid rescue medication (mg) in 72 hours** | | | | | | | | | | | | |
| 3 | randomized trials | seriousc | not serious | not serious | not serious | strong association dose-response gradient |  | | | | ⨁⨁⨁⨁ High |  |

**CI:** confidence interval; **OR:** odds ratio

#### Explanations

a. p-value is 0.497

b. p-value is 0.943

c. Using Rob2 were: 1 low risk, and 2 some concerns