Summary Report

Tetracaine hydrochloride

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Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
BLT	Benzocaine/lidocaine/tetracaine
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
HCl	Hydrochloride
IRB	Institutional Review Board
LET	Lidocaine / epinephrine / tetracaine
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the US Food and Drug Administration (FDA) in its evaluation of the use of tetracaine hydrochloride (tetracaine HCl; UNII code: 5NF5D4OPCI), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how tetracaine HCl is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and health care practitioners were consulted to identify how tetracaine HCl has been used historically and currently.[1-3] Assessments of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of tetracaine HCl and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Tetracaine HCl was nominated for inclusion on the 503B Bulks List by Cantrell Drug Company, Fagron, the Outsourcing Facilities Association (OFA), Pentec Health, Right Value Drug Stores Inc., and the Specialty Sterile Pharmaceutical Society (SSPS). Tetracaine HCl was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Tetracaine HCl was nominated for use as a local anesthetic during eye surgery via an ophthalmic solution in concentrations greater than 1%. In addition, tetracaine HCl was nominated for use as a topical anesthetic in combination with lidocaine and epinephrine (also referred to as LET or LAT) or benzocaine and lidocaine (also referred to as BLT) as a topical gel, cream, solution, and lotion in concentrations of tetracaine HCl ranging from 0.5% to 4%. Tetracaine HCl was also nominated for anesthesia and the treatment of severe pain as a solution for intrathecal injection in concentrations up to 35 mg/mL. Tetracaine HCl was nominated in combination with lidocaine and prilocaine as a dental gel for use as a numbing agent in concentrations of tetracaine HCl ranging from 2% to 4%. Lastly, tetracaine HCl was nominated for use as a liquid for nasal, oral, or topical anesthesia in concentrations ranging for 2% to 4%.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of tetracaine HCl.[6-23]

Reasons provided for nomination to the 503B Bulks List included:

- Children respond better to topical application of the LET gel versus an injection.
- LET is not FDA-approved.
- The current shortages of lidocaine injection have given rise to the use of LET gel for topical anesthesia.
- Invasive eye procedures require the use of a local anesthetic; current practice involves the continuous instillation of eye drops due to low concentration of anesthetic solution, which can lead to the eye overflowing with fluid, leading to loss of active ingredient and procedural complications. Compounding higher-strength solutions will decrease the number of eye drops needed and reduce discomfort to the patient and the surgeon.
- Potocaine® (tetracaine HCl) was discontinued in 2010 by its sole manufacturer for both ophthalmology and rhinolaryngology.

- The compounded product may be the only product to effectively treat the indication for which it is intended.
- Patient need for dosage form or strength, including greater concentration, that is not available commercially.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Manufacturer backorder.
- Practitioners often prescribe doses that require higher strengths or concentrations than those available in FDA-approved products.
- Prescribers often use tetracaine in combination with other medications. However, the sponsors of tetracaine have not pursued FDA-approval for the combination of tetracaine with other medications.
- The FDA Orange Book does not list an injectable tetracaine, but it is available in the market as an ampule. If a compounding pharmacy was going to use an FDA-approved vial for compounding purposes, then the compounding pharmacy would be using the product off-label.
- There is no approved topical anesthetic that contains tetracaine, lidocaine, and prilocaine and their concentrations may be stronger than commercially available products.
- Prescriber or hospital preference for various strengths, combinations with other drugs, volumes and/or final product containers for administration.
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical-size batch for outsourcing facilities; a single vessel compounded from bulk API is safer and more efficient than unmanageable amounts of small vials.
- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100% potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.
- In order to utilize the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of tetracaine HCl products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in the the English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for tetracaine HCl; name variations of tetracaine HCl were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing tetracaine HCl. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed two comprehensive search strategies for both Ovid MEDLINE and Embase. The first search strategy used a combination of controlled vocabulary terms and keywords to describe 2 concepts: tetracaine HCl, and oral, nasal, or intrathecal administration or form. The second search strategy used a combination of controlled vocabulary terms and keywords to describe 3 concepts: tetracaine HCl; topical administration or form; and substances nominated for use in combination with (refer to Appendix 1 for full search strategies). A literature review was not conducted for ophthalmic tetracaine products due to the availability of an FDA-approved product for this ROA. A literature review was not conducted for either single-ingredient topical tetracaine products or some of the nominated topical combinations because these had previously been reviewed (see summary reports for tetracaine February 2020, epinephrine HCl February 2021, and epinephrine bitartrate March 2021). Results were limited to human studies in the English language. Searches were conducted on January 22, 2021. In addition, the ECRI Guidelines Trust® repository was searched on September 11, 2020 for clinical practice guidelines that recommended the use of tetracaine HCl and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.3.3 (Clarivate Analytics) and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which tetracaine HCl was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, preclinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if tetracaine HCl was used as an FDA-approved product in the nominated dosage form, ROA, or combination; a dosage form, ROA, or combination that was not nominated; an unspecified dosage form or ROA; for an indication that was not nominated; used in a combination previously reviewed; mentioned briefly as a previous failed treatment; or tetracaine HCl not used clinically. Studies in which tetracaine HCl was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in

the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of tetracaine HCl; setting; total number of patients; number of patients who received tetracaine HCl; patient population; indication for use of tetracaine HCl; dosage form and strength; dose; ROA; frequency and duration of therapy; use of tetracaine HCl in a combination product; use and formulation of tetracaine HCl in a compounded product; use of tetracaine HCl compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semistructured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances tetracaine HCl was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify medical specialties that would potentially use tetracaine HCl. Potential SMEs were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. Select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided verbal informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

In addition to interviews with individual SMEs, a roundtable discussion with pharmacists was held. Participants were identified through outreach to professional associations that would potentially purchase compounded products from outsourcing facilities. A prequestionnaire was distributed to those who agreed to participate to collect information about the types of facilities at which participants worked and the products they purchased from outsourcing facilities (refer to Appendix 3 for complete survey and *Results of survey* section for results of prequestionnaire). The roundtable lasted 60 minutes and was conducted via Zoom, audio recorded, and professionally transcribed. The transcriptions and notes were synthesized for qualitative data analysis.

Survey

A survey was distributed to the members of professional medical associations to determine the use of tetracaine HCl in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 3 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Years 1 and 2 were not contacted to distribute the project Year 3 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 4 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the US FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Tetracaine HCl is available as an FDA-approved product in the nominated dosage form and ROA. Tetracaine HCl is also available as a 1% solution for injection as an unapproved drug.
- Tetracaine HCl is available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for tetracaine HCl.
- Tetracaine HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia, and the UK.

Table 1. Currently approved products – US[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date[b]
Tetracaine HCl	0.5%	Solution	Ophthalmic	Prescription	2/29/2016
Tetracaine / Lidocaine	7% / 7% 70 mg / 70 mg	Cream, patch	Topical	Prescription	6/23/2005
Tetracaine HCl / Oxymetazoline HCl	6 mg / 0.1 mg per spray	Metered spray	Nasal	Prescription	6/29/2016

Abbreviations: HCl, hydrochloride; US, United States.
[a]Source: US FDA Orange Book: *Approved Drug Products with Therapeutic Equivalence Evaluations*.
[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

Table 2. Currently approved products – select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date[b]
Tetracaine HCl	40 mg/g 5-10 mg/mL 0.5-4%	Eye drops, gel	Ocular, ophthalmic, topical	Abu Dhabi	Active	–
				Australia	S4 – Prescription only medicine	10/30/1991
				Belgium	Medical prescription	10/31/1975
				Canada	Ethical	3/16/1998
				Hong Kong	Pharmacy only	3/20/2006
				Ireland	Pharmacy-only[c] Prescription-only nonrenewable Prescription-only renewable	4/01/1980
				Namibia	–	1/18/1975
				New Zealand	Pharmacy Prescription	11/06/1995
				Saudi Arabia	Prescription	–
				UK	Pharmacy Prescription-only medication	3/05/1987
Tetracaine HCl / Benzocaine / Butamben	2% / 14% / 2%	Liquid	Topical	Canada	Ethical	9/19/1996
Tetracaine HCl / Adrenaline acid tartrate / Lidocaine HCl	0.5% / 0.18% / 4%	Solution	Topical	New Zealand	Restricted	12/21/2006

Tetracaine HCl / Allantoin / Aminochinoride	–	Solution	Buccal	Abu Dhabi	Active	–
Tetracaine / Epinephrine / Lidocaine	500 mg / 180 mg / 4 g	Powder for gel, solution	Topical	Abu Dhabi	Active	–
Tetracaine HCl / Benzocaine	2% / 18%	Cream, gel	Buccal, oral, topical	Canada	Ethical	12/31/1992
				New Zealand	Prescription	10/21/2010
Tetracaine / Lidocaine	7% / 7% 70 mg / 70 mg	Cream, medicated plaster	Cutaneous, ocular, topical	Belgium	Medical prescription	10/19/2008
				Canada	Prescription	9/28/2015
				Hong Kong	Prescription only	7/15/2015

Abbreviations: –, not provided; HCl, hydrochloride; UK, United Kingdom, US, United States.

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in the English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See *Methodology* section for full explanation.

[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

Results of literature review

Study selection

Database searches yielded 2236 references; 0 additional references were identified from searching ECRI Guidelines Trust®. After duplicates were removed, 1406 titles and abstracts were screened. After screening, the full text of 407 articles was reviewed. One hundred forty-two studies were included; after multiple reports of the same study were merged, there were 141 included studies. Two hundred sixty-five studies were excluded for the following reasons: wrong study design (204 studies); nonnominated dosage form or ROA (36); language other than English (7); tetracaine HCl not used clinically (5); FDA-approved dosage form or ROA (4); tetracaine HCl only mentioned briefly (2); nonnominated indication (2); previously reviewed combination (2); wrong substance (2); unable to obtain full text (1).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 141 included studies were published between 1948 and 2020. There were 118 experimental studies, 13 observational studies, and 11 descriptive studies. One study included both descriptive and observational study components.[24] The 141 studies were conducted in the following countries: Australia, Canada, Chile, China, Denmark, France, Germany, Greece, Iran, Israel, Japan, Korea, New Zealand, Norway, Sweden, Switzerland, Taiwan, Turkey, UK, and US.

A total of 37,393 patients participated in the 141 included studies. The number of patients in each study ranged from 1 to 19,672.

Outcome measures differed among the included studies and included: onset, level and duration of anesthesia and analgesia (motor and sensory block); pain score; need for additional sedation or analgesia; blood pressure; and complications.

Refer to Appendix 2 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of tetracaine HCl

All patients received tetracaine HCl for anesthesia/analgesia.

Nineteen thousand five hundred five patients received intrathecal tetracaine HCl, administered in doses ranging from 0.08 mg to 21 mg for 1 to 3 administrations. Patients also received intrathecal tetracaine at a dose ranging from 1 mg/day to 12 mg/day for at least 16 to 21 months.

One thousand two hundred sixty-seven patients received nasal tetracaine HCl, administered in doses ranging from 5 mg to 80 mg for 1-3 sprays.

Two hundred sixty-four patients received oral tetracaine HCl, administered in doses ranging from 5 mg to 18 mg, for either a one-time administration or 8 weeks.

One hundred ninety-nine patients received topical tetracaine HCl, administered for 1 to 4 applications in concentrations ranging from 4% to 6%.

Refer to Tables 6 and 7 for summaries of dosage by indication.

Tetracaine HCl was used as a compounded product and as a combination product (refer to Tables 8-10).

In 20 studies, the authors' concluding statement recommended the use of tetracaine HCl administered via intrathecal, nasal, oral, or topical ROA.[25-44] In 13 studies, the authors' concluding statement did not recommend the use of tetracaine HCl administered via intrathecal, nasal, oral, or topical ROA.[45-57] In 11 studies, the authors concluded that further studies were necessary for the use of tetracaine HCl via intrathecal or topical ROA.[24,58-67] In 5 studies, the authors concluded that intrathecal tetracaine was of similar efficacy to intrathecal bupivacaine interventions.[68-72] In 90 studies, the authors' concluding statement did not address the use of tetracaine HCl for anesthesia/analgesia.[73-162] Two studies recommended the use of tetracaine HCl in nonnominated combinations for oral and topical administrations.[163,164]

Refer to Appendix 2 for a summary of the authors' conclusions.

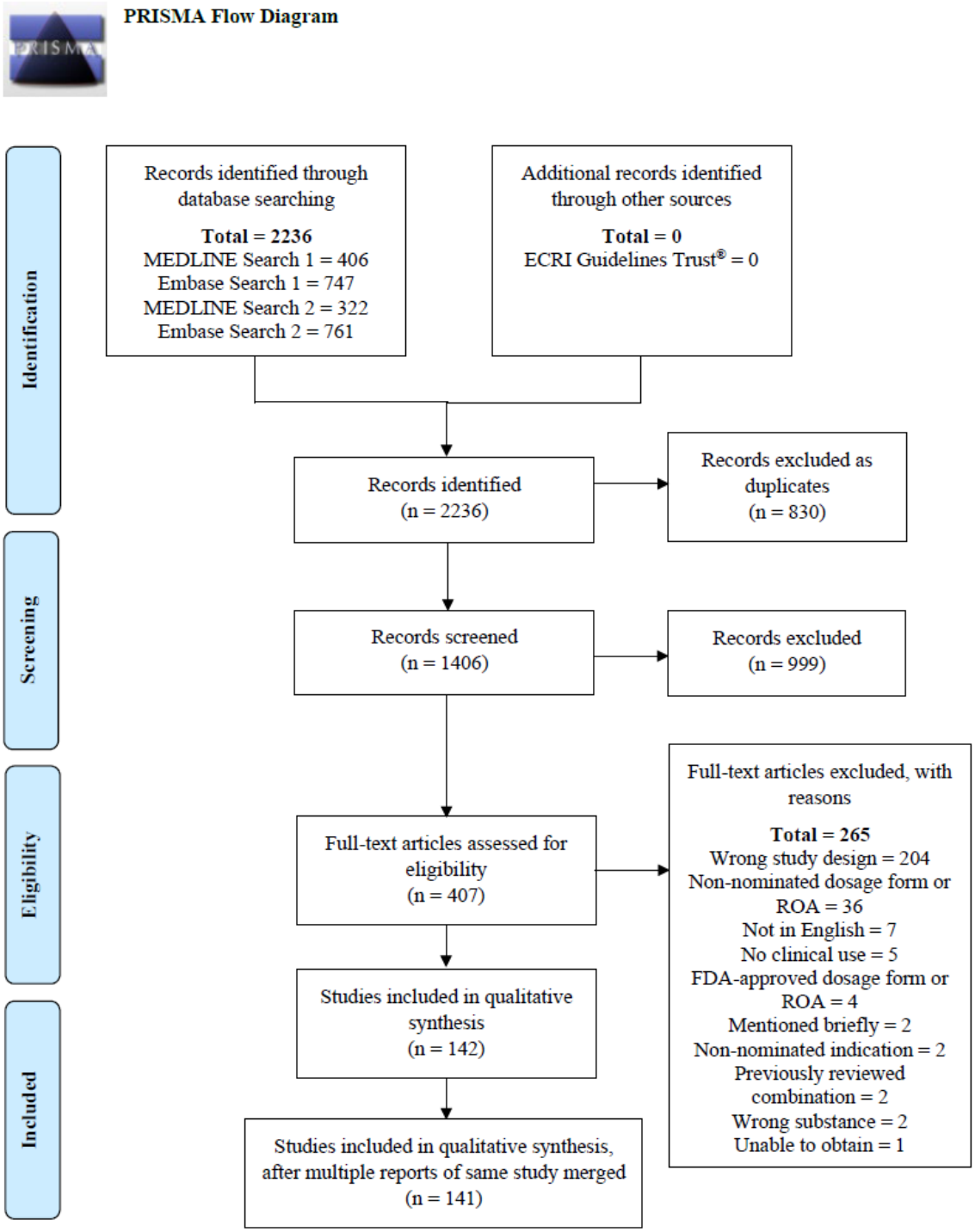
Pharmacology and historical use

Additional references were found that provided information about the pharmacological or historical use of tetracaine HCl.

Tetracaine (also known as amethocaine or Pontocaine) is an ester-type local anesthetic.[165] One use for tetracaine administration is as a topical anesthetic drop into the eye; while tetracaine has shown efficacy in pain relief, research of "case reports of topical anesthetic abuse and misuse, coupled with animal studies, suggest that the use of topical tetracaine could lead to uncommon adverse events," such as corneal toxicity with repeated use.[165] As a result, prolonged patient use of ophthalmic tetracaine is discouraged.[165] In a 2018 retrospective cohort study, authors reviewed the use of tetracaine HCl eye drops dispensed for 24-hour pain relief with simple corneal abrasions, as well as when tetracaine HCl was inappropriately prescribed for complex corneal abrasions.[165] While the authors concluded that larger studies needed to be conducted to confirm the use of topical tetracaine, they added that they "believe a short-term supply of tetracaine should become routine practice in the ED [emergency department] to treat this painful condition, although this recommendation would change should evidence of adverse outcomes be found through further investigation."[165]

In 2021, a report was published on a prospective, double-blind, randomized trial comparing topical tetracaine to the placebo.[166] In this study, patients presenting to the emergency department with uncomplicated corneal abrasions were randomly assigned to receive short-term administration of either tetracaine or placebo.[166] The authors concluded that the 24-hour use of topical tetracaine was safe and effective as an analgesic in patients with uncomplicated corneal abrasions, in addition to being associated with reduced requirement for hydrocodone when compared with the placebo.[166]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	**Number of Studies[a]**
Descriptive[24,27,33,43,61,79,88,106,136,139,147]	11
Observational[24,34,58,63,67,90,99,115,118,125,134,135,155]	13
Experimental[25,26,28-32,35-42,44-57,59,60,62,64-66,68-78,80-87,89,91-98,100-105,107-114,116,117,119-124,126-133,137,138,140-146,148-154,156-164,167]	118

[a]Study 24 counted in both the descriptive and observational total.

Table 4. Number of studies by country

Country	Number of Studies
Australia[35,157]	2
Canada[97]	1
Chile[126]	1
China[44,48,50,121,151]	5
Denmark[53]	1
France[81,82]	2
Germany[49,69]	2
Greece[25,29]	2
Iran[37]	1
Israel[65]	1
Japan[107-109,113,114,123,127-131,140,141,149,150,154,159,160,162]	19
Korea[144,145,161]	3
New Zealand[98]	1
Norway[41]	1
Sweden[47,51,77,78,112]	5
Switzerland[71,72,105]	3
Taiwan[132,152,153]	3
Turkey[93]	1
United Kingdom[119,124,158,167]	3
United States (US)[24,26-28,30-34,36,38-40,42,43,45,46,52,54-64,66-68,70,73-76,79,80,83-92,94-96,99-104,106,110,111,115-118,120,122,125,133-139,142,143,146-148,155,156,163,164]	84
	Total US: 84 Total Non-US Countries: 57

Abbreviation: US, United States.

Table 5. Summary of included studies

Refer to Appendix 2

Table 6. Dosage by indication – US

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Anesthesia/analgesia[24,26-28,30-34,36,38-40,42,43,45,46,52,54-64,66-68,70,73-76,79,80,83-92,94-96,99-104,106,110,111,115-118,120,122,125,133-139,142,143,146-148,155,156,163,164]	Mean 0.65 mg/kg 0.22-2 mg/kg 1-21 mg	0.2-1%	–	Intrathecal	1-3 times
			Crystal, solution		
	1-12 mg/day	–	–		At least 16-21 months
	–	2%	–	Nasal	3 sprays
	5-6 mg		Solution		
	18 mg	3%	Solution	Oral	Once
	–	4-6%	–	Topical	1-4 times
			Cream, gel, ointment		
	15 g/application	4%	Cream		
	–	6%	–		

Abbreviations: –, not provided, US, United States.

Table 7. Dosage by indication – non-US countries

Indication	Dosage	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Anesthesia/analgesia[25,29,35,37,41,44,47-51,53,65,69,71,72,77,78,81,82,93,97,98,105,107-109,112-114,119,121,123,124,126-132,140,141,144,145,149-154,157-162,167]	0.08-20 mg	0.125-1%	–	Intrathecal	Once
			Solution		
	–	0.5%	Drops	Nasal	–
	10-80 mg	0.25-2%	Solution		1-3 sprays
	–	2%	Mouthwash	Oral	8 weeks
	5 mg	1-2%	Spray		Once

Abbreviations: –, not provided, US, United States.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Tetracaine HCl 4% / Benzocaine 20% / Lidocaine 6% – topical cream, gel, lotion, solution • Tetracaine HCl / Benzocaine / Lidocaine – unspecified ROA[80] • Tetracaine HCl 4-6% / Benzocaine 5-20% / Lidocaine 6-8% – topical cream, gel, ointment, unspecified ROA[40,62,66,83,86,106,117,139,147,163]	11
	Tetracaine HCl 0.5% / Epinephrine bitartrate 0.05-0.18% / Lidocaine HCl 4% – topical gel	0
	Tetracaine HCl 2-4% / Lidocaine 5-10% / Prilocaine 5-10% – dental gel • Tetracaine HCl 4% / Lidocaine 10% / Prilocaine 10% – unspecified ROA[55]	1

Table 9. Compounded products – US

Indication	Publication Year	Compounding Method	Dosage Form	Final Strength
Anesthesia/analgesia[62,83,86,163]	2003	"BLT [benzocaine, lidocaine, tetracaine] gel was formulated at a private pharmacy. The proprietary vehicle contains dimethyl sulfoxide and pluronic lecithin organogel (PLO), which help increase absorption through the skin."	Gel	4%
	2012	"Compounded"	–	5%
	2014	"Compounded topical anesthetic"	Ointment	4%
	2017	"Compounded"	Cream	4%

Abbreviations: –, not provided, US, United States.

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

One hundred ninety-nine SMEs were contacted for interviews; 63 agreed to be interviewed, and 136 declined or failed to respond to the interview request. Fourteen SMEs discussed tetracaine HCl. In addition, 3 SMEs that specialized in dermatology and anesthesiology were interviewed in year 1 for a total of 17 SMEs that discussed tetracaine HCl. Amongst these 17 SMEs, there were 10 medical doctors, 3 dentists, 1 dental hygienist, 1 nurse practitioner, 1 pharmacist, and 1 registered nurse. The SMEs specialized and/or were board-certified in allergy, anesthesiology, dentistry, dermatology, oncology, ophthalmology, and pediatrics, working in academic medical institutions, consulting, private practice, inpatient practice, and outpatient practice. The SMEs had been in practice for 1 to 57 years. Additional information was collected as part of the Expanded Information Initiative, referred to as Phase 3, project in which outreach was conducted to the nominators of the bulk drug substances to remedy information gaps in the initial nomination.

Six SMEs discussed the use of tetracaine HCl in ophthalmology. Prior to cataract surgery, a topical anesthetic, along with an antibiotic, phenylephrine, and a dilating drop, are applied to numb the eye. Two of the SMEs stated that they use a commercially available gel formulation of lidocaine as the topical anesthetic and another stated that they use a compounded solution that contains an antibiotic, lidocaine, Mydriacyl® (tropicamide), and a nonsteroidal anti-inflammatory drug. Similarly, prior to retinal surgery, 3 SMEs stated that they administer a few drops of either tetracaine or proparacaine as a topical anesthetic; however, 2 SMEs stated that they use the commercially available formulation.

While tetracaine can be used as a topical anesthetic, the SMEs all stated that it is associated with corneal epithelium toxicity. One SME stated that "if you use too much of it, the cornea takes on a, we call it superficial punctate keratopathy." The SME stated that the only time they use tetracaine is if during cataract surgery the patient starts to have some discomfort or pain when the eye is fixated. In those instances, a Q-Tip can be soaked in tetracaine and administered to the desired area. Two SMEs commented on the use of a higher concentration stating that even with fewer drops the higher strength may still be toxic to the cornea, with 1 SME stating that "whatever concentration is done, corneal toxicity would have to be looked at."

In dentistry, topical numbing agents are typically used to numb the area before the injection of a local anesthetic prior to a procedure. However, there are challenges with using topical numbing agents because there is a risk of the saliva washing them away, causing the product to run down the back of the throat which in turn numbs the throat. There are several commercially available topical numbing agents for use in dentistry. Oraqix® (lidocaine and prilocaine) is a gel commonly used in dental hygiene practice for patients "that are going to be having a gingival procedure and not requiring the use of a drill or cutting into the enamel." One SME stated that this "combination, this is probably the most common one used for the gingival sulcus." Oraqix® also has a thermoset gelling action which makes it "stay in the place you put it" which is especially useful if a vasoconstrictor is not used. EMLA® (lidocaine and prilocaine) is a cream that is not used as commonly in dentistry; 1 SME stated, "I'd say 1 in maybe 20 hygienists might have this in their office, used topically." Most of the SMEs used topical benzocaine when a topical numbing agent is needed, due to its availability. One SME commented that they prefer Cetacaine® (benzocaine/tetracaine/butamben) stating that "it's got a fast onset…lasts a lot longer than say the 20% topical benzocaine that's commonly available just about everywhere."

One SME commented that tetracaine is not used frequently in anesthesia anymore. Tetracaine is available for spinal use, but this would only be used if there was a need for the anesthesia to last a long time. The SME stated that in the past they have used tetracaine for spinal anesthesia in neonates, as these patients clear the drug relatively quickly, but was not sure if this practice was still in use, as the SME does not

currently perform neonatal or pediatric anesthesia. Another SME commented that LET is the preferred product for skin grafts, and that while EMLA® is commercially available, it is only available in 1 concentration so there is a need for compounded products to provide additional options.

Local anesthetics are also commonly used in dermatology prior to a procedure. One SME had used EMLA® previously but does not use it anymore. Prior to laser procedures, a topical anesthetic applied 1-2 hours before the procedure can be useful, however, the SME stated that they do not perform a lot of laser procedures. The SME mostly performs Mohs surgeries, and while a topical anesthetic can be used, "if you inject lidocaine well, there's not a whole lot of injection pain with it. And so there's not a lot of benefit to putting a topical on first—plus the topicals takes time, quite a bit of time actually, to start the numbing. So it's just not efficient to be doing that." The SME mentioned that it would make sense for these products to be stocked in-office as they are administered prior to a procedure and continued that they probably are not going to be using [them] outpatient."

One SME stated that some practitioners like to mix different "caines" together and that this makes sense "because they have different sort of onset of action." The addition of either phenylephrine or epinephrine will prolong the action of the anesthetic as well as keep it localized to the desired area. Practitioners may have their preferred combination products to use but 1 SME stated, "I don't think that there are huge differences in these from what's commercially available. So it's hard for me to imagine that one of these is so much more important. Like that there's a use for one of these that can't be filled by one of the commercially available mixes." The SME also expressed concern with the concentrations included stating that "one of the issues with these, the caines, is that they can cause methemoglobinemia and there have been reports of that occurring after topical application. So, I think that that is a risk, particularly with the sort of higher concentrations. These caines are also metabolized in the same pathway. So, when you ramp up the concentration of both of them, you're really probably risking overloading that the metabolism." Benzocaine is also associated with a risk of cardiotoxicity and so the risk for toxicity would be even higher with the benzocaine/lidocaine/tetracaine formulation. The SME also mentioned that these products have been used prior to tattooing, commenting that some of these products are available OTC. However, the SME would be concerned with potential toxicity because if a large quantity is administered, the drug can be absorbed and become "quite toxic."

Three SMEs were not familiar with the nominated lidocaine/prilocaine/tetracaine combination for use in dental procedures. One SME stated that such a combination "would probably be beneficial if available," but continued that benzocaine is more readily available. Another SME commented that the combination may be useful if a practitioner was trying to avoid toxic dosing by using multiple agents. A third SME stated that since the topical numbing agent is only used to numb the area prior to injecting the local anesthetic, there is not a need for a long-acting topical anesthetic to be used. One SME had worked in a dental office in which a compounded topical anesthetic was used; it was a gel with lidocaine, tetracaine, and butacaine. The SME also commented that some dentists will have a lidocaine 10% / prilocaine 10% / tetracaine 4% / phenylephrine 2% product compounded stating, "Almost every dentist that I've met that will have something compounded, they want lidocaine and tetracaine together in the mix." Including tetracaine in the combination results in a faster onset and a longer duration of action. Additionally, "dental hygiene, it's very bloody," and the addition of a vasoconstrictor, like phenylephrine, can make the patient more comfortable, allow the hygienist to do their job better, reduce the risk of toxicity, and increase the duration of action.

One SME who specialized in pediatrics does not use tetracaine HCl and was not familiar with any of the nominated multi-ingredient products.

As part of Phase 3, 1 nominator provided additional information regarding the multi-ingredient products contained within the tetracaine HCl nomination.

Tetracaine HCl 0.5% / epinephrine 0.05% / lidocaine 4% will be compounded as a topical solution for use as a local anesthetic administered as a 1-time dose. This product is used by practitioners as a non–patient-specific compounded product in clinics, emergency rooms, and hospitals. While there are other local anesthetics available, there are no sterile topical solutions containing epinephrine and 2 anesthetics. LET products have proven to be an effective anesthetic and sterile formulations are the safest for use on an opened wound. The tetracaine products commercially available are not of a sufficient strength to allow for the published formulations of LET to be achieved.

Tetracaine HCl 0.5% / epinephrine bitartrate 0.15% / lidocaine 4% will be compounded as a topical gel for use as a local anesthetic administered as a 1-time dose. This product is used by practitioners as a non–patient-specific compounded product in clinics, emergency rooms, and hospitals. While there are other local anesthetics available, there are no sterile topical solutions containing epinephrine and 2 anesthetics. LET products have proven to be an effective anesthetic and sterile formulations are the safest for use on an opened wound. The tetracaine products commercially available are not of a sufficient strength allow for the published formulations of LET to be achieved.

A roundtable discussion with representatives from a variety of practice settings was held to discuss the use of outsourcing facilities to obtain compounded products. Forty-three participants attended the event; refer to Table 16 for characteristics of the facilities that the participants represented. A prequestionnaire was also distributed to participants; refer to Tables 16-19 for results of the prequestionnaire.

While a majority of the participants purchased some compounded products from an outsourcing facility, the percentage of products obtained varied from less than 1% to the majority of compounded products used at one participant's facility. A participant stated, "We have this method that we use where if we can buy it commercially ready to administer, we do that. If we can't buy it in that format, then we buy it in a vial, for example, that can be snapped into a Mini-Bag Plus because we're a Baxter house, as a second preference. If we can't buy it in either of those two formats and we can get it from a 503B, then we do that. And our last resort is compounding internally." Two participants commented that they will not outsource a product unless 2 outsourcing facilities that they contract with are able to compound the product. This redundancy will allow for a quick flip to the other outsourcing facility if there is an issue with a product compounded from 1 outsourcing facility, minimizing the impact to the participant's facility.

Participants were asked to discuss the decision-making process used at their facility to determine what products to obtain from an outsourcing facility. One major theme that emerged from this discussion was that many of the products purchased from outsourcing facilities are used in critical care areas, like emergency departments and operating rooms. Participants commented that outsourcing facilities are able to provide ready-to-use products that have longer beyond-use dates compared to products compounded in-house, allowing these products to be stocked in automated dispensing cabinets in these units. One participant commented that "we're always going to outsource a PCA [patient-controlled analgesia] syringe because we can store it in a Pyxis machine versus us making it and storing it in a fridge." Another participant commented on the benefits of storing medications in an automated dispensing cabinet, stating that "operationally, if you have a stat medication or something that needs to be delivered within 10 to 15 minutes, if you're looking at us doing it, you're looking at a 5-minute gown and glove. If we don't have somebody in the IV [intravenous] room, if you're doing 797 right, it's 5 minutes. It's 4 minutes to tube it. It's 3 minutes to make it, and then you have a dosage system or a camera system, a few minutes more. We are not able to meet that need or they're just contaminating the IV room if they are trying to do it."

Having ready-to-use products available also minimizes the need for compounding and product manipulations to occur on the floor. This can be especially beneficial in children's hospitals as they face a unique need in that they are already having to perform a lot of manipulations to products due to a lack of concentrations or sizes available. One participant commented that "at baseline, already, we manipulate about 80% of what we dispense to patients" and another stated that "there's a number of drugs that require additional manipulation, to get them to a concentration that's appropriate for kids." One participant stated that "we're trying to minimize compounding, expedite actual therapies to patients in that setting [operating room], minimize manipulations as much as possible." Similarly in the emergency department, one participant stated they prefer ready-to-use products for some floor-stock items, like vasopressor infusions, to prevent compounding from occurring on the floor, and another commented that "we absolutely buy as many pressor drips as we can." One participant remarked that they have received requests from anesthesiologists for products that are commercially available in vials that require manipulation prior to administration to be purchased as syringes from outsourcing facilities stating that "they would prefer to have a syringe form."

Another theme regarding deciding what products to purchase from an outsourcing facility was focused on the utilization and volume of a product that is needed and the overall impact this would have on the pharmacy workload. Critical care areas, like the emergency department and operating room, typically have a high product utilization and overall turnover, leading to several participants obtaining products intended for use in these areas from outsourcing facilities. Participants stated that they evaluate the volume of product needed and the frequency in which that volume is needed compared to the time it would take pharmacy staff to prepare this volume. One participant commented that "we look at the impact that it'll have on staff. If our staff are needing to batch, or if we need to mass produce these in particular to meet the patient demand, then those are the items that we're going to look to potentially move out." Another participant stated that, while they do not obtain a lot of products from outsourcing facilities, "when we do purchase from 503Bs, typically it would be if we just don't have the capacity to keep up with what the demand is." One participant also commented that they will obtain labor-intensive and more complicated products, like epidurals and cardioplegia solutions, from outsourcing facilities to reduce the workload on pharmacy staff. The coronavirus disease 2019 (COVID-19) pandemic has also impacted the operations of hospitals, as noted by 1 participant who stated that "it's just really high volume, and the bigger the hospital, the higher the volume, especially when you have one disease state in half of your hospital" and another who expressed that "without 503B, we would've been in significant trouble." One participant commented that "even though the number might be small [percent of products obtained from outsourcing facilities], some of the reasoning is quite critical, and the amount of time that it saves is very significant for beyond what we're able to do and when." Additionally, challenges with recruiting and retaining pharmacy technicians impact decision-making, with 1 participant stating, "It is not feasible for us to meet the high volume for some common medications to repackage or compound from commercial presentations to a convenient, ready-to-use dosage form or package. The outsourcing facilities thus become a force multiplier, if you will, to offset some of the shortages in staffing."

In addition to the evaluation of the workload on pharmacy staff, the type and capabilities of the facility also impacted the decision-making process. One participant commented that they do not have an established cleanroom and therefore perform sterile compounding in a segregated compounding area. United States Pharmacopeia (USP) <797> standards limit the beyond-use date that can be assigned to these products and, as the participant stated, "We obviously need to provide product with much [more] extensive beyond use dating than we can provide." Several participants also commented that they do not perform high-risk compounding in-house, and therefore, all of these products are outsourced. There are challenges with midsize hospitals being able "to operationalize testing compounds we make for extended

stability." One participant stated, "We might make our own syringes if we could get extended dating, but I believe my operations' colleagues don't always know how to do this and adhere to the letter of the law."

One participant also commented on the impact that The Joint Commission has had on pushing pharmacies to obtain products from outsourcing facilities. The 2018 medication management standard MM.05.01.07 was intended to move IV admixture preparation out of the nursing unit. This forced pharmacies to consider strategies to make IV admixtures available for use on the floor. Additionally, NPSG.03.04.01 states that all medications and solutions should be adequately labeled, including in the operating room and other settings in which procedures are performed. USP <795> and <797> are applicable in operating room settings, stating that products should be labeled and used within 1 hour, which may be problematic if syringes are drawn up at the beginning of the day and cases are canceled or delayed. The participant also commented on the cost related to purchasing premade products from manufacturers, stating that "predatory pricing on premixes is present in the market."

Standardization of products, including concentration, volume, and labeling, was also a driver for obtaining products from an outsourcing facility. However, such standardization may not always be possible. One participant stated that when evaluating similar facilities, you would expect them to have similar needs regarding the concentrations and volumes of products utilized. However, the products utilized in a facility are often developed in-house over decades based on physician and nurse requests, and, more recently, appropriateness for an automated dispensing cabinet. As a result, one participant observed, "These practices had evolved somewhat disparately; even if we had clinical practice guidelines, nobody was putting concentrations into those guidelines and volumes into those guidelines." This has led to challenges with obtaining certain products from outsourcing facilities. As another participant said, "I think we made 9 different epidural concentrations, all driven by anesthesia, and they want what they want and 503Bs may not offer that. No one else in the country is buying that same concentration; a 503B isn't going to go through the expense of adding that to their product list." The participant continued that "similar with the ADCs [automated dispensing cabinets], we've run into situations where dextrose 50% goes on shortage and the 503Bs would be selling it in a syringe. For safety reasons and for crash cart reasons, without having to retrain thousands of nurses of where things are placed, they said, 'No, we can't have it, and that's too big it won't fit,' we want it in this format—and then we're stuck again because there's no 503B offering a format during that shortage that fits where it needs to go. Then we're stuck in sourcing." Additionally, while a commercially available product may be available, the volume may not be appropriate. One participant stated that "3% saline for instance, is sold in a 500 mL bag, but the clinical guideline is a 150 mL bolus. We're either going to draw that out or we're sending it to the ER with stickers all over it saying only give 150 [mL]." The participant continued that "it would be great if the FDA could look at the size of the container that they're approving and whether that's a realistic dose; is it a unit dose or isn't it?"

Participants had differing opinions on the use of outsourcing facilities to obtain drugs during a shortage. Several participants stated that they will typically first restrict use of a drug on shortage, in order to conserve supply, before turning to an outsourcing facility. One participant commented that "most of the time, I will probably pursue restricting, conserving, and looking at all available options prior to going to an outsourcer on my end," and another stated, "I can only think of one time in recent history where we went to an outsourcer." One participant commented that "503Bs can't accept the additional volume if it's a true shortage. If you're not with them preshortage, you're not going to get products when you need it during the shortage," continuing that "typically in a shortage, you learn to live without them. You have to." Additionally, in the event of the shortage being the result of lack of an API, outsourcing facilities are likely to be equally affected and unable to provide assistance. However, one participant stated that they first began working with outsourcing facilities because of shortages. This participant commented that

"what the 503Bs are starting to do, some of the large ones, is that they are also conducting validation studies on API. If sterile becomes short, they quickly switch to producing through API, which ASHP [American Society of Health-System Pharmacists] and the FDA allows." This "adds a lot of flexibility so they can bounce back and forth and really try to insulate us from shortages."

A few participants commented on the use of API by outsourcing facilities. One commented that as long as they are conducting end-product sterility and stability testing and the product meets quality standards, they are not concerned with the starting ingredients. As long as buyers are familiar with regulations and know what to look for, another participant commented, there should not be any issues with purchasing products compounded starting from API. Another participant stated that as more outsourcing facilities began using API, they became more comfortable with them doing so. However, one participant observed that most outsourcing facilities are switching to sterile-to-sterile and only using API if there is a shortage, stating, "I think the FDA has really looked closely at API, and they're slowly pushing the 503B outsourcers to a sterile-to-sterile." Only 1 participant commented that they prefer sterile-to-sterile. Another participant stated that the companies they use are all sterile-to-sterile.

A few participants commented on the need for preservative-free products, particularly in pediatric patients. The example of methadone was provided as it is used for patients with neonatal abstinence syndrome but is only available as a preservative-containing product. So, there is a need for this product to be compounded from API as a preservative-free product. One participant stated that "if there's not a preservative-free containing option, it really should be something that should be able to be compounded from bulk ... especially for the pediatric patient population." However, another participant from a children's hospital stated that the need for a preservative-free option has never been a reason why they have obtained a product from an outsourcing facility. Preservative-free is also an issue for ophthalmic products; however, 1 participant observed this is more on the 503A side. One participant stated that obtaining ophthalmic products from outsourcing facilities has been a challenge and that there are products they would like to obtain from outsourcing facilities but are not able to, forcing them to compound them in-house. This participant also commented that there are 2 outsourcing facilities that compound ophthalmic products, but when they reviewed the facilities, they did not pass their internal quality standards; 1 facility had been banned from distributing products in California by the Board of Pharmacy. There is an additional challenge with obtaining cephalosporins and beta-lactams due to the potential cross-reactivity in patients with allergies. One participant stated that there are some cephalosporins they would like to obtain from an outsourcing facility but cannot because "they would have to build a separate cleanroom with a dedicated HVAC [heating, ventilation, and air conditioning], so you're talking millions of dollars in investment for actually very low volume. Right now, the ROI [return on investment] isn't there." Another participant stated that the concentrations required for ophthalmic antibiotics are not available, but the labor and risk of compounding these products in-house is not worth it.

A few participants commented on purchasing nonsterile products from outsourcing facilities. LET (lidocaine-epinephrine-tetracaine) gel, for use as a topical anesthetic, was the most commonly obtained product along with buffered lidocaine to put in J-Tips. Another participant stated that they obtain diclofenac suppositories from an outsourcing facility due to the high cost of indomethacin suppositories. One participant commented that most of the products they outsource are nonsterile products, generally for oral or topical administration due to a lack of commercially available products being available. The participant stated that they purchase low-dose naltrexone for oral use in patients with refractory fibromyalgia and ketamine troches for patients with chronic pain. The participant continued that, while the evidence does not support many of the ingredients used in topical pain products, "However, there are select patients. It's very rare that taking that cream away from them actually causes more harm than good." A few participants commented that there is a gap in the market for nonsterile products with 1

stating, “I think that there is a large opportunity for more nonsterile products to be produced by 503Bs.” Another stated that as their facility grows and acquires more outpatient clinics, they receive a lot of questions regarding obtaining products for office use. The participant noted that they often have to refer these clinics to outsourcing facilities but stated “There’s not many 503Bs [that] are doing the nonsterile for clinic use.” As a result, the inpatient pharmacy is often asked to take on this role but “you don’t have the space or the staff to do that.”

Based on the responses to the prequestionnaire (refer to *Results of survey*), participants were asked questions regarding specific products obtained from outsourcing facilities. Several participants reported using alum (aluminum potassium) as a bladder irrigation for hemorrhagic cystitis refractory to other treatment options. Participants commented that this is high-risk compounding; they purchase alum from an outsourcing facility because they do not perform high-risk compounding in their facility. One participant commented that their policy states that high-risk compounding is not allowed except for alum. This participant wanted to move away from compounding alum in-house and stated that the addition of aluminum potassium to the bulks list might allow this to happen. Another participant had compounded alum in-house from nonsterile ingredients; however, there had been challenges with crystallization after storage. A few participants commented that there is a sterile alum powder available, which they purchase to compound in-house. One participant had concerns regarding this powder, stating that “I’ve talked to that company, but I’ve had some concerns for them because they don’t sell it as a drug. The owner was selling you a chemical; we’re selling you a bulk API. It’s just sterile. They were fuzzy and I never followed up, but when I asked about their process for verifying the sterility, as you would with a sterile product—we do USP [United States Pharmacopeia] <71> Sterility Testing—they couldn’t really give me an answer. They just say they tested for sterility.” The participants commented that alum is only needed a few times a year. However, as one participant observed, “When you need it, it’s an emergency,” and another noted that it “is a challenge for anybody who has the cyclophosphamide-induced hemorrhagic cystitis.” As a result, one participant maintains a small inventory of alum product that is purchased from an outsourcing facility, but “more times than not, they go unused and expire.” Another stated that they do not keep it in stock because there is a minimum purchase and there are only a few cases a year for whom they need to use alum. The participant had it stat shipped when needed. Another participant stated that “we had a meeting with the head of urology who was baffled why they’re even ordering it. He was like, ‘This is an old, really old. I don’t even know why we’re using it’ and basically approved for us to not even make it anymore for now.”

Two participants commented on the use of glycerin at their facility. One stated that they purchase it from a 503A because they were not able to find an outsourcing facility that provides this product. The participant commented that glycerin is used in 3 different concentrations at their facility, 1 for ophthalmic use, 1 for neurologic use in trigeminal neuralgia, and 1 for instilling into “a very specific kind of pump that’s used to deliver a very specific kind of chemotherapy.” When there are breaks in the chemotherapy regimen, the pump has to be filled with something, and by using glycerin “it can go 3 months or something like that, so it’s a huge patient satisfier to have that concentration available.” The participant also commented that since they have been unable to find an outsourcing facility that compounds the concentration needed for trigeminal neuralgia, they have patients who have been waiting years for treatment. The other participant stated that they compound it in-house but said that it is not done very frequently. The participant commented that it is very difficult to sterilize due to the thickness of the product.

Four participants stated that they obtain sodium citrate as ready-to-use syringes for use as a locking solution in patients undergoing dialysis, with 1 commenting that “our nephrologists, like it in place of heparin for some patients to keep the ports patent or so they don’t have to go to alteplase or some of the

other drugs." There is a commercially available product; however, it is only available as a 500-mL bag and the dose needed is typically less than 30 mL. If the syringes are prepared in-house, then the beyond-use date is limited to 12 to 24 hours depending on storage, which results in waste.

One participant stated that they obtain papaverine from outsourcing facilities for use in urology as Bimix (papaverine/phentolamine) and Trimix (papaverine/phentolamine/alprostadil).

While none of the participants obtained sodium phosphate or aspartic acid from outsourcing facilities for use in cardioplegic solutions, a few commented that they do obtain cardioplegic solutions from outsourcing facilities. The del Nido formulation was the product most commonly obtained. One participant commented that they compound this formulation in-house because the outsourcing facilities did not offer the volume needed at their institution. Another participant commented that while they do obtain the del Nido formulation from an outsourcing facility, they also compound a proprietary formulation in-house. This participant observed that "it is complicated to do in-house. We do it on a Baxa 1200 or 2400, either one, compounder. Then we send it up [sic] for pH and potassium testing. Obviously, then we're confined to 797 beyond-use dates versus longer beyond-use dates that we get from the 503B." Another participant commented that cardioplegic solutions are managed by the perfusion department, not pharmacy, and they use del Nido solution as well as 3 other formulations.

The participants also discussed challenges with utilizing outsourcing facilities. One participant stated that their facility does not use outsourcing facilities because "it just hasn't been financially, not just the money worth it, but just the lead time for how much time you have to give them and how much you have to ... It just isn't worth the dating that they gave us or can give us." Another commented that they obtain very little product from outsourcing facilities due to "the amount of work for vetting and continually validating quality of these 503B outsourcing facilities." The participant stated that they have a robust validation process that takes several months and includes a site visit prior to purchasing from an outsourcing facility, followed by continuous reviewing of quality reports and warning letters. Another challenge has been the reliability of the outsourcing facility. One participant commented that "traditionally, we've found 503Bs to be fairly unreliable, when we have partnered with certain ones, to be able to keep up with the volume. Everybody knows PharMEDium just closed, but we've had some other smaller 503Bs where we've had agreements for certain products to take it off our plate, and then low and behold they're shut down, or closed, or whatever it may be." Minimum purchase amounts were also reported as a concern, with one participant stating that "what we see consistently is the 503Bs, they want us to commit to giving them a certain volume, but then will not give us a reciprocal commitment or at least will not fulfill that reciprocal commitment. That's a huge problem for us making that type of commitment, when we do ultimately have to split our volume in order to make sure that we consistently are able to take care of our patients." Another challenge was related to outsourcing facilities utilizing API to compound narcotics. One participant commented that this often worsens drug shortages due to the quotas that the Drug Enforcement Administration (DEA) places on the quantity that can be produced. The participant stated that "they [outsourcing facilities] want to buy the product that we're trying to buy to take care of our patients today, to sell us tomorrow. We really need the FDA to say that, especially for controlled substances, that 503Bs can consistently prepare those products so that we don't end up with a shortage year after year, after year and then chasing our tail. Also, we may actually want to tell 503Bs, they can't buy those products or that they're limited in the amount of their ability to buy those products to make what are essentially copies of commercially available products, because it actually induces the shortage in many ways."

Results of survey

One person responded to the survey distributed via professional medical associations and available on the project website; refer to Table 11 for respondent characteristics.

Among respondents, 0 (0%) used tetracaine HCl.

A prequestionnaire was distributed to participants of the roundtable discussion (refer to Appendix 3.4 for survey instrument).

Forty-three people responded to the prequestionnaire; refer to Table 16 for respondent characteristics. Amongst respondents, 35 (81% of 43 total respondents) utilized outsourcing facilities to obtain drug products, 4 (9%) did not utilize outsourcing facilities, and 4 (9%) did not respond to this question.

Twenty-seven respondents (19% of 143 responses, where respondents were allowed to select multiple reasons) obtained drug products from outsourcing facilities due to a need for ready-to-use products, and 20 respondents (14%) obtained drug products from outsourcing facilities due to backorders (refer to Table 17).

Fourteen respondents (31% of 45 total responses, where respondents were allowed to select multiple types) obtained nonsterile products from outsourcing facilities and 31 (69%) obtained sterile products from outsourcing facilities. Refer to Table 18 for the categories of products obtained from outsourcing facilities.

Two respondents (2% of 108 responses, where respondents were allowed to select multiple drug products) obtained tetracaine HCl from a 503B outsourcing facility (refer to Table 19).

Table 11. Characteristics of survey respondents

No survey respondents provided this information

Table 12. Compounded products prescribed or administered

Product	**Responses, n (N = 1)**
Acetylcysteine	0
Bupivacaine hydrochloride	0
Clonidine hydrochloride	0
Tetracaine hydrochloride	0
Triamcinolone acetonide	1
Tropicamide	0
None of the above	0

Table 13. Conditions for which tetracaine HCl prescribed or administered

No survey respondents provided this information

Table 14. Reasons for using compounded tetracaine HCl

No survey respondents provided this information

Table 15. Use of non–patient-specific compounded tetracaine HCl

No survey respondents provided this information

Table 16. Demographics of prequestionnaire respondents' facilities

Type of Facility	**Responses, n (N = 102)[a]**
Academic medical center	15
Acute care hospital	16
Children's hospital	8
Community hospital	11
Critical access hospital	2
Dialysis center	2
Federal government hospital	4
Health system	15
Inpatient rehabilitation center	4
Long-term acute care hospital	3
Outpatient surgery center	6
Rural hospital	2
Skilled nursing facility	0
Specialty hospital[b]	4
Trauma center	5
Urban hospital	5
Number of Beds	**Responses, n (N = 39)**

< 50	4
50-99	3
100-199	1
200-299	4
300-399	5
400-599	3
> 600	19

[a]Respondents were allowed to select more than one type of facility.
[b]Specialties provided include cardiology, pulmonary, vascular, home infusion, neurology, psychiatry, and oncology.

Table 17. Reasons for obtaining products from outsourcing facilities

Categories	**Responses, n (N = 143)[a]**
Backorders	20
Convenience	19
Cost	10
Need for concentrations not commercially available	19
Need for multi-ingredient products not commercially available	10
Need for preservative-free products	3
Need for ready-to-use products	27
No FDA-approved product available	7
No onsite compounding facility	1
Onsite compounding facility not equipped to compound all necessary products	19
Other[b]	8

[a]Respondents were allowed to select multiple categories.
[b]Respondents reported staffing shortages, need for extended dating, volume of product used, and standardization projects as additional reasons for utilizing outsourcing facilities.

Table 18. Categories of products obtained from outsourcing facilities

Categories	Responses, n (N = 142)[a]
Cardioplegic solutions	14
Dermatologic preparations	6
Dialysate solutions	0
Fluids	8
Ophthalmic preparations	10
Patient-controlled analgesia	20
Ready-to-use anesthesia syringes	25
Ready-to-use antibiotic syringes and/or bags	14
Ready-to-use electrolyte solutions	5
Ready-to-use vasopressor solutions	18
Total parenteral nutrition solutions	16
Other[b]	6

[a]Respondents were allowed to select multiple categories.
[b]Respondents reported obtaining alum for bladder irrigation, oxytocin, anticoagulant sodium citrate solution, narcotic drips, high-cost antiseizure medications, antiviral medications, topical pain, and oral tablets/capsules.

Table 19. Products obtained from an outsourcing facility

Product	Responses, n (N = 108)[a]
Acetylcysteine	1
Adenosine	2
Aluminum potassium sulfate	2
Aspartic acid	0
Atenolol	0
Atropine	9
Baclofen	4
Betamethasone	0

Biotin	0
Bupivacaine	8
Calcium chloride	1
Caffeine sodium benzoate	0
Cholecalciferol	1
Chromium chloride	0
Clonidine	0
Dexamethasone sodium phosphate	0
Diclofenac	0
Gentamicin	0
Glycerin	1
Hydroxyzine	0
Ketamine	14
Levocarnitine	0
Lidocaine	8
Lorazepam	2
Magnesium sulfate	4
Manganese chloride	0
Methylprednisolone	0
Midazolam	15
Mupirocin	1
Norepinephrine	15
Ondansetron	0
Phytonadione	0
Potassium chloride	0
Potassium phosphate	0

Prilocaine	0
Proline	0
Propranolol	1
Ropivacaine	6
Sodium chloride	0
Sodium citrate	3
Sodium phosphate	0
Tetracaine	2
Triamcinolone acetonide	0
Tropicamide	0
None of the above	8

[a]Respondents were allowed to select multiple products.

CONCLUSION

Tetracaine HCl was nominated for inclusion on the 503B Bulks List as an ophthalmic solution, topical gel, topical cream, topical solution, topical lotion, intrathecal injection, dental gel, and a liquid for nasal, oral, or topical administration for use as a local anesthetic and to treat severe pain. Tetracaine HCl is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Namibia, New Zealand, Saudi Arabia, the UK, and the US.

The literature review included 141 studies; in all of the studies tetracaine HCl was used for anesthesia and analgesia. Tetracaine HCl was used as a compounded product and as a multi-ingredient combination product. Twenty studies recommended the use of tetracaine HCl for anesthesia or analgesia, and 24 studies either did not recommend use or stated that additional studies were needed. The majority of studies did not address the use of tetracaine for anesthesia or analgesia

As made evident in the interviews, tetracaine is used topically in a variety of medical specialties and in multiple practice settings as a local anesthetic prior to a procedure. In ophthalmology, the commercially available formulation was predominately used; however, the SMEs all cautioned that tetracaine HCl is associated with corneal epithelium toxicity and that any strengths formulated would need to be evaluated for this toxicity. In dentistry, 1 SME commented on the use of a combination product that contained 10% / prilocaine 10% / tetracaine 4% / phenylephrine 2%, stating that dentists like to use lidocaine in combination with tetracaine to provide both a quick onset and long duration of action. However, most of the dentists were not familiar with the nominated multi-ingredient combination products. While tetracaine is not used frequently in anesthesiology, it is available for use as a spinal anesthetic for cases that require a long duration of anesthesia. Topical local anesthetics are commonly used in dermatology, but the SME was concerned with the high concentrations for some of the nominated combination products. One SME commented that LET is the preferred agent for skin grafts.

In the survey responses, 0 out of 1 respondent used tetracaine HCl. On the prequestionnaire, 2 respondents obtained tetracaine HCl from a 503B outsourcing facility.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy 1

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to January 21, 2021
- Date last searched: January 22, 2021
- Limits: Humans (search hedge); English language
- Number of results: 406

1	tetracaine/	2612
2	amet?ocain$.tw.	167
3	la#docain$.tw.	0
4	tetocain$.tw.	1
5	tetracain$.tw.	2186
6	or/1-5	3450
7	exp administration, oral/	148,458
8	administration, mucosal/	267
9	administration, intranasal/	14,902
10	infusions, spinal/	160
11	injections, spinal/	12,665
12	oral$.tw.	691,187
13	intraoral$.tw.	13,920
14	buccal$.tw.	28,260
15	mucosal$.tw.	123,121
16	transmucosal$.tw.	1927
17	mucous$.tw.	23,294
18	transmucous$.tw.	12
19	intranasal$.tw.	27,578
20	nasal$.tw.	119,710

21	peridural$.tw.	2076
22	peri dural$.tw.	7
23	caudal$.tw.	46,547
24	intracaudal$.tw.	11
25	intrathecal$.tw.	24,308
26	intra thecal$.tw.	77
27	(nose adj2 (administ$ or appl$ or instill$)).tw.	152
28	nasal sprays/	561
29	oral sprays/	99
30	emulsions/	18,427
31	exp gels/	53,449
32	suspensions/	7840
33	liquid?.tw.	413,474
34	syrup?.tw.	5796
35	elixir?.tw.	656
36	emulsion?.tw.	34,286
37	suspension?.tw.	111,297
38	spray?.tw.	29,112
39	gel?.tw.	312,147
40	(nose adj2 drop?).tw.	252
41	or/7-40	1,924,984
42	and/6,41	585
43	exp animals/ not humans/	4,779,178
44	42 not 43	494
45	limit 44 to english language	406

MEDLINE search strategy 2

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process, and other non-indexed citations and daily 1946 to January 21, 2021
- Date last searched: January 22, 2021
- Limits: Humans (search hedge); English language
- Number of results: 322

1	tetracaine/	2612
2	amet?ocain$.tw.	167
3	la#docain$.tw.	0
4	tetocain$.tw.	1
5	tetracain$.tw.	2186
6	or/1-5	3450
7	administration, topical/	38,826
8	administration, buccal/	992
9	administration, cutaneous/	22,427
10	administration, mucosal/	267
11	skin absorption/	11,838
12	buccal$.tw.	28,260
13	topical$.tw.	108,420
14	transcutaneous$.tw.	14,839
15	epicutaneous$.tw.	2045
16	transdermal$.tw.	14,987
17	((cutanous$ or dermal$ or skin) adj3 (absorb$ or absorpt$ or appl$)).tw.	11,591
18	mucosal$.tw.	123,121
19	mucous$.tw.	23,294
20	transmucosa$.tw.	1928
21	transmucous$.tw.	12
22	dental$.tw.	224,799

23	emulsions/	18,427
24	exp gels/	53,449
25	liniments/	123
26	ointments/	12,859
27	skin cream/	1095
28	liquid?.tw.	413,474
29	emulsion?.tw.	34,286
30	gel?.tw.	312,147
31	liniment?.tw.	148
32	ointment?.tw.	12,138
33	salve?.tw.	344
34	paste?.tw.	12,889
35	unguent$.tw.	114
36	lotion?.tw.	2376
37	cream?.tw.	19,481
38	or/7-37	1,330,745
39	lidocaine/	24,622
40	lidocain$.tw.	22,107
41	lignocain$.tw.	2947
42	exp prilocaine/	2166
43	p#ilocain$.tw.	1612
44	prilocam$.tw.	0
45	propitocain$.tw.	19
46	or/39-45	34,597
47	and/6,38,46	369
48	exp animals/ not humans/	4,779,178

49	47 not 48	341
50	limit 49 to english language	322

Embase search strategy 1

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: January 22, 2021
- Limits: Humans (search hedge); English language
- Number of results: 747

1	‘tetracaine’/mj	3595
2	‘amet$ocain*’:ti,ab,tn	321
3	‘landocain*’:ti,ab,tn	0
4	‘laudocain*’:ti,ab,tn	0
5	‘tetocain*’:ti,ab,tn	8
6	‘tetracain*’:ti,ab,tn	3017
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	5191
8	‘buccal drug administration’/de	702
9	‘oral drug administration’/de	408,127
10	‘mucosal drug administration’/de	468
11	‘intranasal drug administration’/de	15,055
12	‘intraspinal drug administration’/de	3484
13	‘intrathecal drug administration’/de	20,988
14	‘intracaudal drug administration’/de	21
15	‘intraoral*’:ti,ab	18,338
16	‘oral*’:ti,ab	995,923
17	‘buccal*’:ti,ab	36,355
18	‘intranasal*’:ti,ab	37,589
19	‘nasal*’:ti,ab	167,990
20	(nose NEAR/2 (administ* OR appl* OR instill*)):ti,ab	189
21	‘peridural*’:ti,ab	3004
22	‘peri dural*’:ti,ab	12

23	‘caudal*’:ti,ab	60,231
24	‘intracaudal*’:ti,ab	25
25	‘intrathecal*’:ti,ab	36,073
26	‘intra thecal*’:ti,ab	247
27	‘mucosal*’:ti,ab	176,007
28	‘transmucosal*’:ti,ab	2577
29	‘mucous*’:ti,ab	39,351
30	‘transmucous*’:ti,ab	28
31	‘transmucosal drug delivery system’/de	142
32	‘gel’/exp	80,568
33	‘nose drops’/de	789
34	‘nose spray’/de	3293
35	‘oral drops’/de	87
36	‘oral spray’/de	233
37	‘elixir’/de	498
38	‘suspension’/exp	115,698
39	‘syrup’/de	2096
40	‘liquid$’:ti,ab	491,656
41	‘emulsion$’:ti,ab	46,422
42	‘elixir$’:ti,ab	995
43	‘spray*’:ti,ab	54,798
44	‘suspension$’:ti,ab	147,974
45	‘syrup$’:ti,ab	8627
46	‘gel$’:ti,ab	367,563
47	(nose NEAR/2 drop$):ti,ab	416
48	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	2,845,857

	OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47	
49	#7 AND #48	1100
50	[animals]/lim NOT [humans]/lim	6,158,116
51	#49 NOT #50	953
52	#49 NOT #50 AND [english]/lim	747

Embase search strategy 2

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: January 22, 2021
- Limits: Humans (search hedge); English language
- Number of results: 761

1	‘tetracaine’/de	7547
2	‘amet$ocain*’:ti,ab,tn	321
3	‘landocain*’:ti,ab,tn	0
4	‘laudocain*’:ti,ab,tn	0
5	‘tetocain*’:ti,ab,tn	8
6	‘tetracain*’:ti,ab,tn	3017
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	7951
8	‘buccal drug administration’/de	702
9	‘topical drug administration’/de	84,114
10	‘cutaneous drug administration’/de	736
11	‘mucosal drug administration’/de	468
12	‘transdermal drug administration’/de	9269
13	‘topical treatment’/de	13,675
14	‘skin absorption’/de	8155
15	‘buccal*’:ti,ab	36,355
16	‘topical*’:ti,ab	153,518
17	‘transcutaneous*’:ti,ab	19,971
18	‘epicutaneous*’:ti,ab	3474
19	‘transdermal*’:ti,ab	21,953
20	((cutaneous* OR dermal* OR skin) NEAR/3 (absorb* OR absorpt* OR appl*)):ti,ab	18,326
21	‘mucosal*’:ti,ab	176,007
22	‘mucous*’:ti,ab	39,351

23	‘transmucosa*’:ti,ab	2581
24	‘transmucous*’:ti,ab	28
25	‘dental*’:ti,ab	248,111
26	‘transmucosal drug delivery system’/de	142
27	‘cream’/de	9770
28	‘gel’/exp	80,568
29	‘liniment’/de	256
30	‘lotion’/de	2956
31	‘ointment’/exp	18,952
32	‘paste’/de	2543
33	‘salve’/de	170
34	‘cream$’:ti,ab	30,467
35	‘emulsion$’:ti,ab	46,422
36	‘gel$’:ti,ab	367,563
37	‘liniment$’:ti,ab	241
38	‘lotion$’:ti,ab	4107
39	‘ointment$’:ti,ab	21,944
40	‘paste$’:ti,ab	15,419
41	‘salve$’:ti,ab	485
42	‘unguent*’:ti,ab	242
43	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42	1,225,778
44	‘lidocaine’/de	77,349
45	‘lidocain*’:ti,ab,tn	30,987
46	‘lignocain*’:ti,ab,tn	4123
47	‘prilocaine’/de	4720

48	‘prilocain*’:ti,ab,tn	2325
49	‘psilocain*’:ti,ab,tn	0
50	‘prilocam*’:ti,ab,tn	0
51	‘propitocain*’:ti,ab,tn	53
52	#44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51	83,062
53	#7 AND #43 AND #52	903
54	[animals]/lim NOT [humans]/lim	6,158,116
55	#53 NOT #54	842
56	#53 NOT #54 AND [english]/lim	761

Appendix 2. Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Indication: Analgesia/anesthesia					
Abajian et al, 1984, US[58]	–	78 Patients undergoing operative procedures • High-risk (gender not specified, mean 92 days ± [SEM] 8) • Congenital anomaly (gender not specified, mean 168 days ± [SEM] 52) • Term (gender not specified, mean 57 days ± [SEM] 7)	Spinal anesthesia with tetracaine was attempted in all patients • High risk (36) • Congenital anomaly (8) • Term (26) Spinal anesthesia was abandoned in 8 of the term patients due to inability to obtain cerebrospinal fluid (CSF)	Level and duration of anesthesia	"Our results show that spinal anesthesia can be safely and reliably performed in these infants. The technique has not resulted in hypotension or bradycardia and no complications have occurred. However, the superiority of spinal to other forms of anesthesia in this group of patients remains to be demonstrated."
Abboud et al, 1985, US[59]	–	52 Patients scheduled for elective cesarean section • General anesthesia (0%, mean 29.4 y ± 1.6) • Spinal anesthesia (0%, mean 27.9 y ± 1.2) • Epidural anesthesia (0%, mean 28.2 y ± 1.1)	• General anesthesia (20) • Spinal anesthesia with tetracaine, dextrose, and epinephrine (18) • Epidural anesthesia with 2-chloroprocaine and epinephrine (7) • Epidural anesthesia with lidocaine and epinephrine (7)	Appearance, pulse, grimace, activity, and respiration (APGAR) scores; neurologic and adaptive capacity score (NACS)	"It is concluded from our study that the NACS that has been used recently to evaluate neonatal effects of obstetric medications is a valid and sensitive examination for neurobehavioral performance, and that general anesthesia for cesarean section is more depressant than regional anesthesia during the first few hours of life. Because these findings may have minimal effects on a healthy infant, a high risk neonate may be adversely affected by general anesthesia and further work is needed to evaluate the effect of general and regional anesthesia on high risk neonates."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Abboud et al, 1983, US[73]	–	40 Patients undergoing cesarean section • General anesthesia (0%, mean 25.8 y +/ 5.6) • Regional anesthesia (0%, mean 25.7 y ± 11.8)	• General anesthesia (14) • Spinal anesthesia with tetracaine, dextrose, and epinephrine (14) • Epidural anesthesia with bupivacaine (2) • Epidural anesthesia with 2-chloroprocaine (4) • Epidural anesthesia with lidocaine (6)	Maternal plasma β-endorphin levels	"In conclusion, data from our study demonstrate that general anesthetic induction in patients undergoing cesarean section is associated with an increase in plasma β-endorphin levels. This increase appears to be a manifestation of a stress response of the endocrine system."
Armstrong et al, 1983, US[74]	Double-blind study	30 Patients scheduled for transurethral resection of the prostate or other urological procedures on the perineum (100%, mean 71 y)	Intrathecal administration of 1 of the following: • Tetracaine (10) • Tetracaine plus epinephrine (10) • Tetracaine plus phenylephrine (10)	Level of anesthesia and analgesia and the time to maximum height	"Our results clearly show that phenylephrine, in the dose used, produced a clinically useful prolongation of tetracaine spinal anesthesia. Epinephrine, on the other hand, only produced a useful prolongation in the lower segments, and not in the T12 dermatome."
Aston et al, 1963, US[75]	–	40 Patients scheduled for minor surgical procedures (gender not specified, range 16-82 y)	Anesthesia with 1 of the following: • Thiamylal (6) • Cyclopropane (5) • Intrathecal tetracaine (13) • Halothane (16)	Venous 5-hydroxytryptamine (5HT) levels	"The suggestion is made that, since many of these patients were allowed to ventilate spontaneously, an increase in venous 5HT may have been due to respiratory acidosis. Transient, but severe, depression of hepatic function may also have contributed to such a finding. Decrease in 5HT blood levels may have been the result of induced sympathetic blockade with splanchnic pooling."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Atchison et al, 1989, US[76]	Prospective, double-blind study	20 Patients undergoing total hip arthroplasty (gender and age not specified)	Intrathecal hypobaric tetracaine plus epinephrine: • Fast injection (10) • Slow injection (10)	Anesthetic levels, duration of anesthesia, and specific gravities of injectate and CSF	"Slow injection of hypobaric tetracaine through a 22-gauge Whitacre needle produces lower levels of spinal anesthesia that tend to be of longer duration than levels resulting from fast injection."
Axelsson et al, 1985, Sweden[78]	–	21 Patients scheduled for urological surgery, cystoscopy, minor biopsies • Bupivacaine 0.75% (100%, mean 67.3 y ± 2.4) • Bupivacaine 0.5% (100%, mean 70.4 y ± 1.2) • Tetracaine (100%, mean 67.4 y ± 1.4)	Spinal anesthesia with 1 of the following: • Bupivacaine 0.5% (7) • Bupivacaine 0.75% (7) • Tetracaine (7)	Onset, level, and regression of analgesia, urodynamic study, muscle strength	"With normal hydration during the operation, the urine production during spinal anaesthesia is of such magnitude that there is a risk of prolonged overdistension of the bladder. To avoid protracted postoperative bladder symptoms, careful supervision of the bladder function is of great importance inpatients receiving spinal anaesthesia with long-acting local anaesthetics."
Axelsson et al, 1985, Sweden[77]	–	36 Patients scheduled for urological surgery, cystoscopy or transurethral resection of a tumor in the urinary bladder • Bupivacaine 0.75% (gender not specified, mean 67.8 y ± 1.81) • Bupivacaine 0.5% (gender not specified, mean 65.9 y ± 1.65) • Tetracaine (gender not specified, mean 68.6 y ± 1.64)	Intrathecal administration of 1 of the following: • Bupivacaine 0.75% (11) • Bupivacaine 0.5% (14) • Tetracaine (11)	Onset and regression of motor block	"The motor block curves gave a good idea of the onset and regression of the motor block in the lower extremities during spinal anesthesia. The motor block curves revealed a difference in regression of the block between the types of movement, and showed that glucose-free bupivacaine solution gave longer complete motor block, which also regressed later than in the patients who received the hyperbaric solutions of bupivacaine and tetracaine. The difference between the level of analgesia and the level of motor block was most evident in the lower lumbar and upper sacral segments."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Beer et al, 2014, US[163]	Multicenter, open-label, randomized, split-face study	51 Patients undergoing filler injections for the correction of nasolabial folds (2%, median 49 y)	• Food and Drug Administration–approved anesthetic cream containing lidocaine 7% and tetracaine 7% (51) • Compounded ointment containing benzocaine 20%, lidocaine 6%, and tetracaine 4% (51)	Subject-reported visual analog scale (VAS) scores, investigator assessment of subject pain	"LT [Lidocaine and tetracaine] cream is an effective and safe alternative to use with filler injections for the correction of nasolabial folds."
Berger et al, 1987, US[79]	Report of a case	1 Patient with multiple sclerosis presenting for elective insertion of an inflatable penile prosthesis (100%, 53 y)	• Intrathecal tetracaine and morphine (1)	Spinal block	"While our case represents only a single case report, it does demonstrate that a combination of spinal and general anesthesia may be appropriate, and can be administered safely to a patient with long-standing but relatively stable multiple sclerosis. In addition, if regional anesthesia is selected, the addition of intrathecal morphine does not increase risk.
Biesman et al, 2009, US[80]	–	10 Patients with mild to moderate photo damage and moderate wrinkles undergoing facial resurfacing (gender not specified, mean 58 y)	• Full-face, single-pass confluent 2,790-nm treatment followed by 120 mL, 2-3 pass fractional 2,790-nm treatment of areas with wrinkles and/or laxity (10) All patients received topical anesthesia with benzocaine, lidocaine, and tetracaine with or without oral anesthesia	Pain level, adverse events	"The combination of single treatment confluent and fractionally ablative 2,790 nm laser modalities for facial resurfacing is well tolerated and safe and appears to be effective in the treatment of common stigmata of moderate to advanced photoaging."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Bigler et al, 1986, US[45]	–	40 Patients undergoing elective inguinal hernia repair (100%, mean 54 y ± 3)	Spinal anesthesia with either: • Hyperbaric bupivacaine (20) • Hyperbaric tetracaine (20)	Extent of blockade, blood pressure and heart rate, plasma catecholamines	"It is concluded that spinal anesthesia with 3ml of hyperbaric 0.5% tetracaine is followed by a more pronounced fall in blood pressure compared to identical dose of bupivacaine. The more pronounced sympathetic blockade, confirmed by plasma catecholamine measurements, following tetracaine is probably due to a higher cephalad spread of neurogenic blockade, rather than a differential effect on sympathetic nerve fibres."
Bonnet et al, 1989, France[81]	–	44 Patients scheduled for orthopedic surgery • Saline (64%, mean 45.6 y ± 15.2) • Clonidine 75 mcg (47%, mean 40.8 y ± 21.9) • Clonidine 150 mcg (40%, mean 49.6 y ± 18.2)	Intrathecal tetracaine plus: • Saline (14) • Clonidine 75 mcg (15) • Clonidine 150 mcg (15)	Level and duration of sensory and motor blockade	"Clonidine appears to be an alternative to epinephrine to prolong the duration of hyperbaric tetracaine spinal anesthesia in humans, confirming data reported with spinal bupivacaine. The effect of clonidine is dose dependent."
Bonnet et al, 1988, France[82]	–	43 Patients scheduled for orthopedic surgery of the lower limbs • Water (33%, mean 43.8 y ± 20.1) • Dextrose (46.2%, mean 47.4 y ± 19.6) • Dextran (46.2%, mean 52.6 y ± 18.6)	Intrathecal tetracaine plus: • Water (15) • Dextrose (13) • Dextran (13)	Sensory and motor block, pain scores	"The results of the current study point out that isobaric tetracaine is not more efficient than hyperbaric solutions to prevent TP [tourniquet pain] and that anesthesia induced by both types of tetracaine solutions is not solid enough to reduce the frequency of TP."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Boonsiri et al, 2017, US[83]	Single-site, double-blind, paired study	31 Patients undergoing augmentation of their facial wrinkles (9.68%, mean 54.35 y ± 11.89)	Topical cream containing benzocaine, lidocaine, tetracaine (BLT) with: • Smooth particles (31) • Abrasive particles (31) Study was conducted in a split-face fashion	VAS scores, Wong-Baker Face Pain Rating Scale	"Conclusion: The study demonstrated that subjects experienced a higher mean pain level (but not statistically significant) when using the BLT with smooth texture compared to the BLT with abrasive particles when applied before HA [hyaluronic acid] dermal filler injection."
Boswell et al, 1992, US[60]	–	15 Patients admitted for elective surgical implantation of spinal cord stimulators (60%, mean 51 y)	Spinal anesthesia with either: • Lidocaine (14) • Tetracaine (1)	Spinal cord conduction	"In summary, the predominant site of action of usual clinical doses of subarachnoid lidocaine and tetracaine appeared to be at spinal rootlets, although partial block of afferent spinal cord conduction was also observed. Because these observations may not apply to other local anesthetics, comparative studies are warranted."
Bourolias et al, 2010, Greece[25]	Prospective study	48 Patients undergoing transnasal fiber-optic laryngoscopy (44%, mean 38 y)	Intranasal administration of 1 of the following: • Lidocaine (24) • Tetracaine (24)	VAS scores	"Topical tetracaine is efficacious and safe for anesthesia of the nasal mucosa and can provide ideal conditions. On the basis of these findings, we recommend tetracaine solution as the first choice of transnasal fiber-optic laryngoscopy (TFL)."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Bray et al, 1948, US[84]	–	119 Patients receiving radium implantation for cervical carcinoma (0%, age not specified)	Intrathecal dibucaine or tetracaine plus either: • Phenylephrine (not specified) • Ephedrine (not specified) • Epinephrine (not specified)	Blood pressure, ability to move lower extremities, block duration	"Epinephrine is by far superior to ephedrine or neosynephrine when used intrathecally with either, Pontocaine or nupercaine. Both sensory anesthesia and motor paralysis are potentiated. The pressor effect with either drug is negligible. No neurological changes were noted."
Bridenbaugh et al, 1982, US[85]	Randomized, double-blind basis	100 Patients scheduled to undergo transurethral resection of the prostate (100%, age not specified)	• Intrathecal tetracaine prepared from crystals and epinephrine (50) • Intrathecal tetracaine prepared from liquid and epinephrine (50)	Onset and duration of anesthesia, height of block	"From this study, the conclusion reached must be that the clinical impressions which have developed concerning the differences noted, or believed by various anesthetists, concerning crystalline vs liquid tetracaine solution have more to do with familiarity with a technique than the form in which tetracaine is supplied."
Brightman et al, 2012, US[86]	Single-center, prospective open-label study	10 Patients with evidence of facial volume loss and skin laxity (gender and age not specified)	• Topical anesthesia with compounded benzocaine 20%, lidocaine 6%, and tetracaine 5%, facial nerve blocks, and tumescent anesthesia on the lateral face before using microneedle fractional bipolar radiofrequency system (10)	Subjective and objective facial skin tightening and increase in volume	"With this pilot study, subjective and objective facial skin tightening and increase in volume was achieved at one month, with continued improvement seen at three and four month follow up, following one treatment session with the microneedle fractional bipolar radiofrequency system."
Brooker et al, 1997, US[87]	Prospective, double-blind, randomized, cross-over study	13 Patients scheduled for elective surgery (77%, mean 62.5 y)	Intrathecal tetracaine plus sequential infusions of: • Epinephrine (13) • Phenylephrine (13)	Blood pressure, heart rate, stroke volume	"We reject our hypothesis that epinephrine more completely and effectively restores baseline conditions after spinal anesthesia than phenylephrine."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Broster et al, 1987, US[88]	Case reports	2 Patients with epidermolysis bullosa presenting for elective cesarean section (0%, range 17-30 y)	Spinal anesthesia with • Tetracaine (1) • Bupivacaine (1)	Sensory block	"In summary, we report two patients with EB [epidermolysis bullosa] who underwent cesarean section. They were successfully anesthetized with regional anesthesia, and we give a brief review of suggested anesthetic management for these difficult patients. We believe regional anesthesia should be considered in EB patients to prevent airway manipulation."
Brown et al, 1980, US[89]	–	60 Patients undergoing elective gynecological or general surgery to the lower trunk or legs • 10 mg (gender not specified, mean 48.07 y ± 2.79) • 15 mg (gender not specified, mean 51.73 y ± 3.14)	Intrathecal tetracaine of 1 of the following: • 10 mg (30) • 15 mg (30)	Onset, spread, regression and duration of sensory and motor block	"While it seems that the differences between hypobaric, isobaric and hyperbaric solutions are related to their density and the effects of gravity, the contribution of viscosity should not be ignored. Solutions made hyperbaric by the addition of dextrose are considerably more viscous than hypobaric or isobaric solutions which are prepared in water or saline. Thus there may be less tendency for the drug to diffuse into and become diluted by the cerebrospinal fluid, thus allowing it to spread further in a relatively concentrated state. The difference in the anaesthetic pattern seen with hyperbaric solutions could be related to this."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Brull et al, 1989, US[68]	–	51 Patients scheduled for elective surgery • Bupivacaine (90%, mean 64.8 y ± 11.95) • Tetracaine (82%, mean 58.4 y ± 13.83)	Spinal anesthesia with 1 of the following: • Bupivacaine (29) • Tetracaine (22)	Onset, maintenance, and regression of anesthesia	"In summary, this study shows that at equivalent doses, hyperbaric spinal bupivacaine and tetracaine are similar with respect to mean maximal rostral spread, that width of the zones of differential blockade to light touch, pinprick, and temperature modalities is constant during onset, maintenance, and regression of spinal anesthesia, and that the choice of local anesthetic does not influence hemodynamic parameters."
Burke et al, 1978, US[90]	–	1063 patients who underwent laparoscopy (gender and age not specified)	Spinal anesthesia with 1 of the following: • Tetracaine (not reported) • Lidocaine (not reported) Some patients received epinephrine as well, if laparotomy was contemplated	Complications	"In conclusion, spinal anesthesia for laparoscopy appears to be well tolerated, safe and satisfactory. Spinal anesthesia provides excellent and reliable relaxation as well as quiet breathing and can be administered with significant freedom from morbidity and mortality."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Caldwell et al, 1985, US[91]	–	30 Patients scheduled for lower extremity surgery, prostate resection, vaginal hysterectomy, or inguinal hernia repair • Tetracaine (gender not specified, mean 58.5 y ± 13.6) • Tetracaine and epinephrine (gender not specified, mean 65.7 y ± 10.8) • Tetracaine and phenylephrine (gender not specified, mean 67.1 y ± 6.9)	Spinal anesthesia with 1 of the following: • Tetracaine (not reported) • Tetracaine and epinephrine (not reported) • Tetracaine and phenylephrine (not reported)	Onset of anesthesia, duration of sensory and motor block	"In summary, we have demonstrated that phenylephrine significantly prolongs sensory anesthesia to a greater extent than epinephrine in higher, clinically useful doses with tetracaine spinal anesthesia. This information may be useful in deciding whether to choose epinephrine or phenylephrine when planning spinal anesthesia for various surgical procedures on the lower extremities."
Carpenter et al, 1989, US[92]	–	60 Patients undergoing transurethral resection of the prostate • Tetracaine 6 mg and epinephrine (100%, mean 68.6 y ± 7.3) • Tetracaine 6 mg (100%, mean 70.5 y ± 8.4) • Tetracaine 10 mg and epinephrine (100%, mean 68.0 y ± 8.0) • Tetracaine 10 mg (100%, mean 72.7 y ± 7.0)	Spinal anesthesia with 1 of the following: • Tetracaine 6 mg and epinephrine (20) • Tetracaine 6 mg (20) • Tetracaine 10 mg and epinephrine (10) • Tetracaine 10 mg (10)	Sensory level of anesthesia, success rate of anesthesia, nausea	"In conclusion, we anticipate that epinephrine will also improve the effectiveness of a low dose of tetracaine for other operations. A larger dose of tetracaine may be equally effective, yet produce higher dermatomal levels of spinal anesthesia and is more likely to cause adverse side effects."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Celik et al, 2013, Turkey[93]	Randomized, prospective study	80 Patients who underwent septoplasty (53.75%, mean 28 y ± 2)	Merocel sponge removed after either • 24 hours (20) or • 48 hours (20) Merocel sponge in a glove finger and removed after either • 24 hours (20) or • 48 hours (20) Merocel sponge was moistened with tetracaine	Morbidities, normal breathing time	"The main morbidities after septoplasty usually occur during removal of nasal tampons causing pain and bleeding. A nasal tampon within a glove finger decreases these morbidities by preventing adhesion to neighboring structures. In addition, there is no requirement for removal of tampons more than after 24 hours post-operatively. Earlier removal increases patient comfort. However, as mentioned, studies on the advantage of transseptal suturing in terms of pain have been reported and the efficacy has been well described. Therefore, combining transseptal suturing and a nasal tampon within a glove finger might be more effective for successful surgery and less postoperative morbidity."
Chamberlain et al, 1986, US[94]	–	20 Patients undergoing minor urologic procedures (gender and age not specified)	Spinal anesthesia with 1 of the following: • Tetracaine (10) • Lidocaine (10)	Upper level of sensory blockade, skin temperature	"We therefore conclude that sympathetic blockade up to the T-1 level is only partial. It is possible that Greene's method detects the level of total sympathetic blockade and that our method demonstrates the upper limit of partial blockade, and the four-segment difference between our results and Greene's could be explained in anatomic terms, for it is well recognized that overlap of three or more segments occurs in sympathetic innervation."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Chantigian et al, 1984, US[26]	–	21 Patients undergoing elective cesarean delivery (0%, age not specified)	Intrathecal tetracaine mixed with one of the following: • Dextrose (10) • Procaine (11)	Onset and duration of sensory and motor block	"We have, at the writing of this paper, performed cesarean sections with tetracaine-procaine on 500 patients and have found it very satisfactory."
Ciancio et al, 2016, US[164]	Randomized, double-masked, multicenter Phase 3 clinical trial	110 Patients undergoing a dental procedure in a maxillary nonmolar tooth • K305 spray (32%, mean 37.1 y ± 14.73) • Tetracaine spray (64%, mean 31.3 y ± 12.01) • Placebo spray (46%, mean 35.7 y ± 14.64)	All products were intranasal sprays applied ipsilaterally to the treatment tooth • K305 spray containing tetracaine and oxymetazoline (44) • Tetracaine-only spray (44) • Placebo spray (22)	Completion of the procedure without rescue local anesthetic	"In this study, combination tetracaine–oxymetazoline nasal spray was superior to tetracaine-only and placebo sprays in producing anesthesia sufficient to allow completion of a direct dental restorative procedure on a maxillary nonmolar tooth in adults. This novel compound could offer a valuable alternative to injected local anesthesia for patients and practitioners alike."
Concepcion et al, 1988, US[46]	Randomized, prospective study	40 Patients undergoing orthopedic surgery of lower extremities • Bupivacaine (90%, mean 62.2 y ± 14.8) • Tetracaine (70%, mean 64.4 y ± 8.5)	Intrathecal administration of 1 of the following: • Bupivacaine (20) • Tetracaine (20)	Levels and duration of sensory anesthesia, motor blockade, occurrence of tourniquet pain	"Tourniquet pain is a frequent occurrence during an otherwise adequate spinal anesthetic. However, this phenomenon occurs less frequently when bupivacaine is employed for spinal anesthesia as compared to tetracaine. This difference in the incidence of tourniquet pain between the two drugs is unrelated to baricity, dosage, or level of sensory anesthesia."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Concepcion et al, 1984, US[95]	Randomized, double-blind study	50 Patients undergoing orthopedic surgeries involving lower extremities • Tetracaine (40%, mean 33.9 y) • Tetracaine with epinephrine 0.2 mg (60%, mean 54.8 y) • Tetracaine with epinephrine 0.3 mg (40%, mean 57 y) • Tetracaine with phenylephrine 1 mg (20%, mean 53.4 y) • Tetracaine with phenylephrine 2 mg (80%, mean 61.1 y)	Intrathecal administration of 1 of the following: • Tetracaine (10) • Tetracaine plus epinephrine 0.2 mg (10) • Tetracaine plus epinephrine 0.3 mg (10) • Tetracaine plus phenylephrine 1 mg (10) • Tetracaine plus phenylephrine 2 mg (10)	Duration of sensory and motor blockade	"The results show that both vasoconstrictor agents in the doses used significantly prolong duration of sensory anesthesia and motor blockade produced by the subarachnoid administration of tetracaine. At equipotent doses no differences existed between the ability of epinephrine and phenylephrine to prolong the duration of spinal anesthesia produced by tetracaine."
Cope et al, 1986, US[27]	Case report	1 Patient with myotonic dystrophy undergoing cesarean section (0%, 24 y)	• Intrathecal tetracaine in divided doses plus topical local bupivacaine (1)	Sensory and motor block	"The combination of spinal with topical local anesthesia applied directly to the uterus may be a valid alternative approach to avoid a major problem associated with anesthesia in the myotonic parturient."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Corke et al, 1982, US[96]	–	31 Patients scheduled for elective cesarean section • Non-hypotensive (0%, mean 29 y ± 1.6) • Hypotensive (0%, mean 29 y ± 1.7)	• Intrathecal tetracaine (31)	Occurrence of hypotension, neonatal acid-base levels	"In conclusion, a short period of hypotension (less than 2 minutes) frequently associated with spinal anaesthesia for Caesarean section although altering the maternal and neonatal acid-base values, does not appear to affect the neurobehavioural performances of the newborn. Therefore, adequate prehydration, uterine displacement and prompt diagnosis and treatment of hypotension appear to be important."
Cunningham et al, 1983, Canada[97]	–	24 Patients undergoing transurethral resection of the prostate (100%, mean 68.2 y ± 7.1)	• Intrathecal tetracaine (12) • Intrathecal tetracaine with morphine (12)	Efficacy of anesthesia and analgesia, occurrence of side effects	"For patients undergoing transurethral resection of the prostate the addition of morphine 1 mg to spinal anaesthesia with amethocaine produces excellent surgical anaesthesia and postoperative analgesia. However, the disadvantages of the technique are evident. The danger of delayed respiratory depression must be considered and may preclude the use of this technique unless the patient can return to a recovery room or intensive care unit."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Davis et al, 1989, New Zealand[98]	–	122 Patients undergoing total hip replacement for osteoarthritis (gender and age not specified)	• Intrathecal tetracaine (65) • General anesthesia (57)	Leg blood flow	"However, no clear or consistent relationships could be demonstrated in the present study between specific changes in leg blood flow or venous resistance and the occurrence of DVT [deep vein thrombosis] in individual patients, even though there was an overall halving of the DVT rate in the SAB [spinal anesthesia] group compared with the GA [general anesthesia] group."
Doleys et al, 1998, US[99]	–	36 Patients with non-cancer pain, implanted with Synchromed infusion system (67%, mean 45.61 y)	• Intraspinal infusion therapy with tetracaine and morphine (36)	Changes in pain, functioning, work and oral narcotic use	"The results support the potential utility of infusion therapy in the treatment of non-cancer pain. This treatment, however, is not without problems and should be applied judiciously and in the context of evolving guidelines."
Drakeford et al, 1991, US[100]	Prospective, randomized, double-blind study	60 Patients scheduled to have elective total hip or knee arthroplasty (48.3%, mean 64 y)	Intrathecal tetracaine, epinephrine plus 1 of the following: • Control (20) • Morphine (20) • Hydromorphone (20)	Pain scores, postoperative analgesics	"The additional use of subarachnoid administration of narcotics simultaneous with that of spinal anesthetic in these patients who had a total joint arthroplasty of the lower extremity enabled them to be awake, alert, and comfortable, with minimum pain, during the first twenty-four hours after the operation."
Dubelman et al, 1979, US[101]	–	16 Patients presenting for urological surgery (100%, range 49-83 y)	After receiving subarachnoid tetracaine, patients were asked to • Cough three times (8) or • Not cough (8)	Mean upper level of analgesia	"We conclude that three vigorous coughs do not influence the spread of spinal anesthesia."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Egbert et al, 1960, US[102]	–	137 Patients undergoing elective surgery upon the abdominal wall or lower extremities (100%, range 18-79 y)	Intrathecal tetracaine plus epinephrine in 1 of the following doses: • 0 mg (22) • 0.1 mg (21) • 0.2 mg (18) • 0.3 mg (29) • 0.4 mg (24) • 0.5 mg (23)	Duration of analgesia	"The inability to predict the duration of spinal anesthesia in individual patients with reasonable accuracy would seem to preclude an attempt to obtain analgesia for a definite length of time with a particular dose of epinephrine."
Endler et al, 1985, US[61]	Case reports	4 Patients who underwent laparoscopy for in vitro fertilization (0%, range 29-40 y)	• Intrathecal tetracaine (4)	Sensory level; need for additional medication; length of procedure; complications	"We report our experience in managing anesthesia in four patients in whom we used a subarachnoid block. Ova were obtained in three patients, and two became pregnant and delivered healthy full-term infants. Although the high pregnancy rate was noted with delight, it is clearly a statistical happenstance. It would be interesting, however, to carry out prospective studies to determine whether a relationship between the incidence of pregnancy and anesthetic method might exist."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Finkel et al, 2002, US[103]	Prospective, randomized study	14 Patients undergoing repair of either uncomplicated atrial or ventricular septal defects • Hyperbaric morphine (gender not specified, mean 49.3 months ± 25.8) • Hypobaric morphine (gender not specified, mean 38 months ± 15.8)	Intrathecal tetracaine plus either • Hyperbaric morphine (7) or • Hypobaric morphine (7)	Pain scores, incidence and severity of side effects	"In summary, the findings of this preliminary study suggest that the injection of hypobaric intrathecal morphine sequentially after hyperbaric tetracaine spinal anaesthesia in cardiac patients given light general anaesthesia reduces the incidence of side effects compared with the combined injection of intrathecal morphine and tetracaine (hyperbaric morphine mixture) patients positioned in Trendelenburg for at least 10 min following intrathecal injection."
Forbes et al, 1978, US[104]	–	27 Patients undergoing operative procedures (gender not specified, range 27-89 y)	• Intrathecal tetracaine (20) • Intrathecal tetracaine and epinephrine (7)	Sensory block	"Our findings do not support Urban's description of a straight-line recession of spinal analgesia. But, since the literature does not support the concept of a straight-line "spinal cord dermatome", the cord remains a possible site of receding spinal analgesia."
Gaggero et al, 1993, Switzerland[105]	–	45 Patients undergoing elective prosthetic hip surgery • Glucose 1 mL (80%, mean 85 y ± 5) • Glucose 2 mL (80%, mean 85 y ± 4) • Glucose 4 mL (67%, mean 82 y ± 5)	Intrathecal tetracaine plus 1 of the following • Glucose 1 mL (15) • Glucose 2 mL (15) • Glucose 4 mL (15)	Maximum sensory level, characteristics of anesthesia	"In conclusion, the results of the present study indicate that the volume of injectate does not affect the characteristics of hyperbaric spinal anesthesia when the dose of local anesthetic remains constant."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Gaviola et al, 2013, US[28]	Prospective, randomized, double-blind study	99 Patients undergoing transnasal endoscopy (52.5%, mean 58.0 y ± 16.2)	Intranasal oxymetazoline followed by intranasal topical anesthetic with either • Tetracaine (49) or • Lidocaine (50)	VAS scores	"In patients undergoing transnasal endoscopy, use of either 2% tetracaine or 4% lidocaine has similar effect. Tetracaine may be a better choice in older patients, however."
Gielen et al, 1984, Sweden[47]	Double-blind study	80 Patients scheduled for urologic surgery, orthopedic surgery on lower limbs, or inguinal hernia repair • Bupivacaine 0.5% (70%, mean 61.6 y ± 2.4) • Bupivacaine 0.5% plus glucose (60%, mean 60.7 y ± 2.2) • Bupivacaine 0.75% (80%, mean 58.6 y± 2.2) • Tetracaine plus glucose (80%, mean 56.3 y ± 2.1)	Intrathecal administration of: • Bupivacaine 0.5% (20) • Bupivacaine 0.5% plus glucose (20) • Bupivacaine 0.75% (20) • Tetracaine plus glucose (20)	Onset and duration of motor blockade, duration of analgesia	"In conclusion, the hyperbaric bupivacaine solutions with their relatively moderate blockade of the lower limbs are suitable for urologic surgery, but less suitable for orthopedic surgery. On the other hand, the glucose free bupivacaine solutions that produced a similar or longer duration of analgesia and a more profound motor blockade than hyperbaric bupivacaine solution, should be most useful for orthopedic surgery."
Goldstein et al, 2019, US[106]	–	3 Patients with persistent genital arousal disorder (PGAD; 0%, range 10-14 y)	• Topical application of benzocaine, lidocaine, and tetracaine (3)	Reduction of persistent genital arousal disorder symptoms	"PGAD is not limited to afflicting adults, however the current definition needs to evolve to include children with the disorder. Similar to the assessment of an adult with PGAD, a detailed biopsychosocial assessment should be considered in young PGAD patients. Significant findings included psychologic concerns, low androgen hormone values, and abnormal vulvoscopy, especially within the vestibule."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Goyagi et al, 1996, Japan[108]	–	26 Patients scheduled for total abdominal hysterectomy • Clonidine (0%, mean 47 y ± 2) • Control (0%, mean 46 y ± 1)	Intrathecal tetracaine and morphine, followed by either • Oral clonidine (13) or • Control (13)	Duration of analgesia, motor block	"In conclusion, oral clonidine premeditation 5 mcg/kg resulted in prolongation of the time to the first request for supplemental analgesics, and a decrease in the number of patients who required supplemental analgesics during 48 h after abdominal total hysterectomy under spinal anesthesia with hyperbaric tetracaine 12 mg plus morphine 0.2 mg. Oral clonidine preanesthetic medication also prolonged the duration of motor block by tetracaine spinal anesthesia. However, oral clonidine premeditation did not enhance the adverse effects of intrathecal morphine."
Goyagi et al, 1995, Japan[107]	–	36 Patients scheduled for gynecologic surgery • Epinephrine, morphine and tetracaine (0%, mean 41 y ± 2) • Morphine and tetracaine (0%, mean 46 y ± 1) • Epinephrine and tetracaine (0%, mean 44 y ± 3)	Spinal anesthesia with tetracaine plus 1 of the following: • Epinephrine and morphine (11) • Morphine (13) • Epinephrine (12)	Pain scores, time to first request for supplemental analgesics	"In conclusion, coadministration of intrathecal epinephrine (120 mcg) and morphine (200 mcg) in tetracaine spinal anesthesia resulted in prolongation of the time to the first request for analgesics, and in the decrease in the number of injected supplemental analgesics during 48 h after gynecologic surgery. Moreover, the addition of epinephrine did not enhance the adverse effects of intrathecal morphine, such as nausea, pruritus, and respiratory depression. Therefore, the addition of epinephrine provides better postoperative analgesia by intrathecal morphine after gynecologic surgery."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Goyagi et al, 1998, Japan[109]	–	41 Patients undergoing surgical procedures • Control (25%, mean 45 y ± 15) • Clonidine (29%, mean 45 y ± 12)	Intrathecal tetracaine plus either • Oral clonidine (21) or • Control (20)	Blood pressure, heart rate, upper dermatomal level of analgesia	"In conclusion, an IV bolus injection of ephedrine 0.2 mg/kg effectively counteracted hypotension during spinal anesthesia in patients who received oral clonidine premeditation 5 mcg/kg. The pressor effect of ephedrine was augmented in clonidine-treated patients."
Guinard et al, 1992, US[110]	Prospective study	137 Patients undergoing transurethral resection of the prostate (TURP) • Sensations (100%, mean 69.5 y ± 10.4) • No sensations (100%, mean 70.9 y ± 7.7)	Intrathecal administration of 1 of the following: • Tetracaine 6 mg (46) • Tetracaine 10 mg (30) • Bupivacaine (61) Epinephrine or sterile water was randomly added to each solution	Occurrence of sensations at the operative site	"In conclusion, we think that patients should have the opportunity to choose between spinal and general anesthesia, with equal guarantees of success and comfort. We have shown that a failure rate of spinal anesthesia under 1% can be accomplished for TURP. Perhaps this is influenced by meticulous technique and judicious use of intravenous sedation and supplementation."
Gutsche et al, 1976, US[111]	–	17 Patients undergoing elective repeat cesarean section (0%, age not specified)	Intrathecal tetracaine after intramuscular (IM) administration of • Ephedrine and procaine (8) or • Procaine (9)	Blood pressure	"The prophylactic IM administration of ephedrine might, however, be contraindicated in essential hypertension or hypertension secondary to toxemia of pregnancy."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Hahn et al, 1993, Sweden[112]	–	40 Patients undergoing urological operations • Epidural mepivacaine and adrenaline (100%, mean 72 y ± 6) • Epidural bupivacaine (100%, mean 72 y ± 8) • Intrathecal tetracaine (100%, mean 64 y ± 8)	• Epidural mepivacaine and adrenaline (20) • Epidural bupivacaine (10) • Intrathecal tetracaine (10)	Hypotension, blood concentrations of hemoglobin and glucose	"In conclusion, the present study provides indirect support for the view that the pronounced haemodilution regularly seen in patients who develop arterial hypotension in connection with the induction of EDA [epidural anesthesia] is caused by a Starling mechanism and not by hyperglycaemia or high-level analgesia."
Hajiioannou et al, 2010, Greece[29]	Prospective study	48 Patients undergoing submucosal diathermy of the inferior turbinate (52%, mean 35 y)	Neurosurgical sponges inserted under the roof of the nose with either: • Tetracaine solution (24) • Lidocaine spray (24)	Pain scores	"Topical tetracaine is an efficacious and safe topical anaesthetic for nasal mucosa that is ideal for nasal surgery. However, the importance of using an adequate and safe dose along with careful monitoring during and after use cannot be overemphasized. On the basis of these findings, we recommend tetracaine solution as the first choice anaesthetic for submucosal inferior turbinate diathermy."
Han et al, 2020, China[48]	Prospective, assessor-blind, randomized controlled trial	60 Patients scheduled for either endoscopic submucosal dissection or peroral endoscopic myotomy • Dyclonine hydrochloride mucilage (53.3%, median 55 y) • Tetracaine (56.67%, median 54.5 y)	• Novel awake intubation care with dyclonine hydrochloride mucilage (30) • Standard awake intubation with tetracaine oral spray (30)	Mean arterial pressure	"In awake endotracheal intubation, novel care using oral dyclonine hydrochloride mucilage can provide more favorable mucosal anesthesia and better intubation conditions than standard of care using oropharyngeal tetracaine sprays."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Harnik et al, 1986, US[30]	–	20 Patients undergoing inguinal hernia repairs using spinal anesthesia (gender not specified, mean 28.19 weeks ± 2.2)	• Spinal tetracaine (20)	Onset, duration, and recovery of blockade	"We conclude that subarachnoid blockade with hyperbaric tetracaine for the repair of inguinal hernias is a satisfactory alternative to general anesthesia in our hands for selected premature infants."
Hoff et al, 1994, US[31]	–	60 Patients undergoing vascular bypass surgery on the lower extremities • 15 mg (gender not specified, mean 71.3 y ± 8.5) • 12 mg (gender not specified, mean 63.2 y ± 13.8) • 10 mg (gender not specified, mean 65.2 y ± 12.5)	Intrathecal tetracaine plus bupivacaine with both drugs at a dose of either: • 15 mg (8) • 12 mg (11) • 10 mg (41)	Onset and duration of sensory block, blood pressure, side effects	"Spinal anesthesia using bupivacaine and tetracaine mixed in a single injection technique can last 5 hours at the T12 level without added untoward effects when compared with lower-dose spinal anesthetics."
Hoshi et al, 1999, Japan[113]	–	34 Patients scheduled to undergo spinal anesthesia for elective knee surgeries • Early oral feeding (EOF; 81%, mean 26 y ± 10) • Nothing by mouth (60%, mean 32 y ± 13)	Intrathecal tetracaine, followed by either: • EOF (16) • Nothing by mouth (15)	Appetite before first meal, time to first gas emission, time to first defecation, side effects	"In conclusion, our preliminary study suggests that EOF including regular hospital meals can be well tolerated in young and healthy subjects undergoing minor surgical procedures under spinal anesthesia."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Inoue et al, 2004, Japan[114]	–	96 Patients scheduled to undergo elective surgical procedures in the lithotomy (urological surgery) or supine position (orthopedic surgery) • Lithotomy (96%, mean 69 y ± 6) • Lithotomy and epinephrine (96%, mean 64 y ± 9) • Supine (67%, mean 61 y ± 11) • Supine and epinephrine (71%, mean 60 y ± 13)	Lithotomy position with intrathecal administration of either • Tetracaine (24) or • Tetracaine and epinephrine (24) Supine position with intrathecal administration of either • Tetracaine (24) or • Tetracaine and epinephrine (24)	Extent of sensory blockade, need for atropine for bradycardia	"In conclusion, intrathecal epinephrine in the supine position enhanced the cephalad spread of sensory block levels by hyperbaric tetracaine compared with hyperbaric tetracaine alone in the lithotomy position. This additional extent of sensory blockade was two segments."
Janik et al, 1989, Germany[49]	–	80 Patients scheduled for transurethral resection of the prostate • Bupivacaine in 5% glucose (100%, mean 65.7 y ± 1.5) • Bupivacaine in 8% glucose (100%, mean 68.6 y ± 1.3) • Tetracaine in 5% glucose (100%, mean 68.7 y ± 1.7) • Tetracaine in 8% glucose (100%, mean 69.3 y ± 1.6)	Spinal anesthesia with 1 of the following: • Bupivacaine in 5% glucose (20) • Bupivacaine in 8% glucose (20) • Tetracaine in 5% glucose (20) • Tetracaine in 8% glucose (20)	Onset and regression of sensory and motor blockade	"In conclusion, our results indicate that for transurethral surgery, 0.5% bupivacaine 4 ml in 5% glucose provides a rapid and controllable spread of sensory analgesia of optimal duration associated with a complete motor blockade of moderate duration. Unless a more intense motor blockade of longer duration is wanted, in which case an 8% glucose solution is recommended, bupivacaine with 5% glucose is proposed for transurethral surgical procedures."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Janik et al, 1989, Germany[69]	–	80 Patients scheduled for transurethral resection of the prostate • Tetracaine (100%, mean 67.8 y ± 1.6) • Tetracaine with barbotage (100%, mean 70.8 y ± 1.9) • Bupivacaine (100%, mean 70.1 y ± 1.3) • Bupivacaine with barbotage (100%, mean 67.9 y ± 1.4)	Spinal anesthesia with 1 of the following: • Tetracaine (20) • Tetracaine with barbotage (20) • Bupivacaine (20) • Bupivacaine with barbotage (20)	Cephalad spread of analgesia, motor block	"In conclusion, when using hyperbaric tetracaine 0.5% for spinal analgesia, we recommend the routine use of barbotage, since the onset of sensory blockage is significantly faster compared with a single injection. Barbotage with hyperbaric bupivacaine 0.5%, however, has the advantage of shortening the onset time of complete motor blockade."
Jichao et al, 2016, China[50]	Prospective, single-blind, randomized study	932 Patients undergoing electronic flexible laryngoscopy (EFL) • Oral dyclonine hydrochloride mucilage (ODHM; 44%, mean 44.5 y ± 12.0) • Tetracaine spray (43%, mean 44.7 y ± 12.1)	• ODHM (466) • Tetracaine nasal spray (466)	VAS scores to assess comfort	"A single use of ODHM seems to be superior to three doses of TS [tetracaine spray] in patients undergoing EFL, specifically in procedures longer than 100 s."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Johnson et al, 1972, US[115]	–	42 Patients receiving labor analgesia (0%, age not specified)	• Local or no anesthesia with lidocaine (6) • Pudendal block anesthesia with lidocaine (12) • Spinal block with tetracaine (12) • Peridural block with lidocaine (12)	Intrauterine pressure, superimposed voluntary effort	"However, under the study conditions, maximum coaxing both before and after the anesthesia results in decreased voluntary effort in some individuals after loss of the 'bearing down' reflex that may result in prolongation of the second stage of labor. These findings must be considered when selecting an anesthetic agent for the patient in labor and tend to reinforce the concept that the ideal anesthetic for childbirth is yet to be found."
Kalman et al, 1995, Sweden[51]	–	33 Patients scheduled for inguinal hernia repair • Halothane-diethyl-ether anesthesia (100%, mean 59 y) • Halothane anesthesia (100%, mean 58 y) • Spinal anesthesia (100%, mean 58 y)	• General anesthesia with halothane-diethyl-ether (11) • General anesthesia with halothane (11) • Spinal anesthesia with tetracaine (11)	Liver cell metabolism, cell integrity, synthesizing capacity, cholestasis, global liver function	"In summary, the present study shows no major alterations in liver function during the early postoperative period following brief HE [halothane-diethyl-ether] azeotrope anesthesia for minor surgery. Our findings support our view that halothane-diethyl-ether could be considered as an alternative general anaesthetic agent for use under field conditions."
King et al, 1995, US[116]	–	83 Patients who received isobaric tetracaine (gender not specified, range 13-68 y)	• Intrathecal tetracaine (83)	Level of anesthesia	"Although not a formal study, our data support the results of Hirabayashi and colleagues who concluded that the higher anaesthesia level in adolescent patients with hyperbaric spinal anaesthesia was probably caused by a flatter thoracic curvature. This problem does not arise with an isobaric anaesthetic solution which may therefore be preferable in adolescent patients."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
King et al, 1995, US[32]	–	120 Patients scheduled for orthopedic surgery of the lower limbs • Tetracaine 10mg/mL (84%, mean 36 y ± 7) • Tetracaine 10 mg/2 mL (78%, mean 34 y ± 8) • Tetracaine 15 mg/2 mL (88.6%, mean 39 y ± 6) • Tetracaine 20 mg/2 mL (81%, mean 37 y ± 5)	Intrathecal tetracaine at concentration of 1 of the following: • 10 mg/1 mL (30) • 10 mg/2 mL (30) • 15 mg/2 mL (30) • 20 mg/2 mL (30)	Onset, duration, and peak of blockade	"We conclude that in tetracaine isobaric spinal anesthesia, an increase in the volume led to greater range of initial spread and neural block. When the volume remained constant, the duration of the neural block and to a lesser extent, the peak level of anesthesia increased as the drug dose increased. Therefore, the numerous variables must be considered in predicting the effects of spinal anesthesia. Alteration in the technique as well as patient factors may produce different results."
Knight et al, 2016, US[117]	–	20 Patients undergoing skin rejuvenation (10%, mean 47.5 y ± 6.1)	• Three full-face synergistic sequential treatment (SST) of intense pulsed light (IPL), followed immediately by non-ablative fractional laser (NAFL) All subjects were pretreated with cream containing benzocaine 20%, lidocaine 6%, and tetracaine 4%	Goldman-Fitzpatrick Wrinkle and Elastosis Scale	"Both investigator and subjects noticed a significant improvement in fine-lines, skin texture, pigmentation, tightness and brightness. At the 6-month follow-up, overall improvement was assessed as 'Improved' to 'Very Much Improved' by 94% of the of the subjects and 65% of subjects demonstrated 'Good' to 'Very Good' satisfaction with the treatment."
Kubal et al, 1991, US[33]	Case report	1 Patient with Friedreich's ataxia scheduled for elective cesarean section (0%, 31 y)	• Intrathecal tetracaine plus epinephrine (1)	Duration of anesthesia, sensory level, vital signs	"In summary we described a case of Friedreich's ataxia in which spinal anesthesia was successfully used for cesarean section."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Lambert et al, 1982, US[118]	–	78 Patients with spinal cord injuries (gender and age not specified)	Sedation with diazepam, fentanyl, alphaprodine, pentobarbital, or some combination thereof (8) • Topical lidocaine (2) • No anesthesia (9) • Halothane/O_2 (7) • Halothane/N_2O/O_2 (3) • Enflurane/O_2 (1) • Morphine/O_2 (1) • Innovar/N_2O/O_2/relaxant (1) • Intrathecal lidocaine (21) • Intrathecal tetracaine (25)	Systolic blood pressures	"It has become our policy to elect low spinal anesthesia in patients at risk for autonomic hyperreflexia unless there are contraindications. The data presented here support our belief that interrupting the afferent loop of the autonomic hyperreflexia reflex arc with low spinal anesthesia is logical, effective, easily performed, easily controlled, and causes little or no morbidity. For most procedures, sacral anesthesia is adequate and the amount of anesthetic agent required is small."
Leder et al, 1997, US[52]	Prospective, double-blind, randomized study	202 Patients undergoing flexible fiberoptic endoscopy evaluation of swallowing (FEES; 51.5%, range 18-86 y)	Nasal administration of 1 of the following: • Tetracaine (54) • Ephedrine (50) • Placebo (48) No intranasal administration (50)	Comfort-discomfort rating	"A topical anesthetic or vasoconstrictor does not need to be administered to the nasal mucosa prior to transnasal endoscopy. This allows speech-language pathologists to perform a FEES independently. In addition, performing a FEES without prior treatment eliminates any potential adverse anesthetic reactions and assures a reliable physiologic evaluation. A comfortable examination will result when the endoscope is inserted into the most patent naris by a trained endoscopist, for example, a physician or speech-language pathologist."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Lee et al, 1988, UK[119]	–	40 Patients undergoing lower-limb urological or hernia surgery • Dextrose 0% (40%, mean 44 y ± 10.6) • Dextrose 1.25% (40%, mean 46 y ± 12.3) • Dextrose 2.5% (30%, mean 46 y ± 12.8) • Dextrose 5% (30%, mean 49 y ± 9.2)	Intrathecal tetracaine in 1 of the following: • Dextrose 0% (10) • Dextrose 1.25% (10) • Dextrose 2.5% (10) • Dextrose 5% (10)	Cephalad extent of block	"Spinal solutions of the specific gravity used in this study do not give blocks in which the mean cephalad spread is lower than that associated with the use of commercially available products. It is not apparent why present hyperbaric spinal solutions have a specific gravity and tonicity far exceeding that of cerebrospinal fluid, as this would appear to be unnecessary. The use of solutions containing even lower concentrations of dextrose may merit investigation."
Lee et al, 1950, US[34]	–	300 Patients undergoing urological surgery (gender and age not specified)	• Intrathecal tetracaine and neosynephrine (300)	Anesthesia	"A method of spinal anesthesia with 'heavy' Pontocaine and intrathecal neosynephrin is described which is admirably suited for transurethral surgical procedures by reason of production of profound anesthesia of certain long duration without untoward side effects. It is noteworthy that the patients reported in this study were of the age group of urological practice and among whom were many poor cardiovascular risks."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Lee et al, 2003, US[62]	Prospective study	30 Volunteers being evaluated for local anesthesia with laser pain (gender and age not specified)	All patients received each product on different test sites of their arm: • Control (30) • Benzocaine, lidocaine, and tetracaine gel (30) • EMLA containing lidocaine and prilocaine with and without occlusion (30) • Lidocaine cream (30) • Lidocaine microemulsion gel (30)	Pain scores	"This BLT [benzocaine 20%, lidocaine 6%, tetracaine 4%] gel in a vehicle containing permeation enhancers can provide effective cutaneous anesthesia as early as 15 minutes after application without occlusion. Anesthesia reached a maximum 30 minutes after application. Other studies are needed to compare BLT gel with other topical anesthetics, with and without occlusion."
Levin et al, 1980, US[120]	Randomized, blind-observer study	103 Patients undergoing surgery (gender and age not specified)	Spinal anesthesia with either: • Hyperbaric tetracaine (52) • Isobaric tetracaine (51)	Sensory block	"We conclude that simple mechanical and physical factors (e.g. barbotage, gravity) are not as important in determining the subarachnoid spread of anesthetic solutions as has been believed."
Li et al, 2009, China[121]	Prospective, randomized, double-blind clinical study	30 Patients undergoing endoscopic sinus surgery (63%, mean 38 y)	Nasal administration of either: • Tetracaine with adrenaline (15) • Tetracaine (15)	Blood pressure, mean arterial pressure, heart rate	"As most clinical observations, including ours, did not measure the plasma concentration, we can only compare changes in BP [blood pressure] and HR [heart rate]. The reason might be that the different plasma concentrations of adrenaline resulted in the activation of different sympathetic receptors; ultimately, a faster HR with or without hypotension could be observed."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Liu et al, 1997, US[122]	Randomized, double blind, cross-over fashion	12 Healthy volunteers undergoing evaluation of the efficacy of epinephrine test doses (83%, mean 37 y)	Intravenous epinephrine plus intrathecal administration of either1 of the following: • Lidocaine (12) • Tetracaine (12) • Bupivacaine (12)	Blood pressure, heart rate	"In summary, it does not appear that reductions in SBP [systolic blood pressure] and HR [heart rate] responses to intravenous injection of epinephrine during spinal anesthesia will clinically affect the efficacy of epinephrine test doses during combined spinal epidural anesthesia in young, healthy adults. Peak HR response to epinephrine usually occurred within 60 seconds and may be a more consistent indicator than peak SBP response."
Logan et al, 2002, Australia[35]	–	38 Patients with head and neck cancer undergoing radiotherapy (gender and age not specified)	Chlorhexidine mouthwash plus: • Tetracaine mouthwash (not reported) • Placebo mouthwash (not reported)	Hospitalization, degree of mouth discomfort, general well-being, general activity	"From the results of this study, it can be concluded that amethocaine hydrochloride did have some beneficial effect on pain associated with radiation-induced oral mucositis based on the fact that: The use of amethocaine hydrochloride resulted in significant improvement in the appetite of patients who were undergoing radiotherapy for head and neck cancer compared with patients who used a placebo mouthwash. The use of amethocaine hydrochloride significantly enabled patients who were undergoing radiotherapy for head and neck cancer to eat a wider variety of foods (that is, solid versus liquids) compared with patients who used a placebo mouthwash."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Louthan et al, 1965, US[36]	–	84 Patients undergoing anorectal surgery (50%, range 17-90 y)	• Intrathecal tetracaine (84)	Onset and level of anesthesia	"This technic appears to offer a satisfactory, simple, and safe method of performing spinal anesthesia for anorectal surgery."
Madineh et al, 2017, Iran[37]	Randomized controlled trial	62 Patients undergoing septoplasty • Tetracaine (88%, mean 18.28 y) • Distilled water (83%, mean 37.31 y)	Intranasal administration of either • Tetracaine drops (32) or • Distilled water drops (30)	Postoperative pain, hemodynamics	"According to results of the study, local anesthetic by tetracaine drop can be a safe and effective way in reducing pain after septoplasty surgery. Thus, it is recommended to use this drop to reduce pain in the septoplasty surgery."
Marstrand et al, 1985, Denmark[53]	Double-blind study	20 Patients scheduled for urological surgery • Bupivacaine (90%, mean 67.9 y ± 3.03) • Tetracaine (100%, mean 70.9 y ± 2.41)	Spinal anesthesia with either • Bupivacaine (10) or • Tetracaine (10)	Level and duration of sensory analgesia, onset and duration of complete motor block	"It is concluded that 0.75% plain bupivacaine 3 ml is a good alternative to hyperbaric 0.5 % amethocaine with glucose in urological surgery of longer duration. The cardiovascular changes were less, and the durations of sensory analgesia and motor blockade were longer in the bupivacaine group."
Martinson et al, 1948, US[63]	–	167 Patients undergoing spinal anesthesia for unspecified procedures (31.3%, range 18-82 y)	Dextrose and ephedrine plus tetracaine at 1 of the following doses: • 3 mg (1) • 4 mg (2) • 5 mg (22) • 6 mg (21) • 7 mg (6) • 8 mg (107) • 10 mg (8)	Duration of analgesia, complications	"In a reported series of 167 cases no serious complication was encountered and the incidence of minor undesirable reactions did not appear to be increased by this procedure. It is felt that the results of this comparatively small series are sufficiently encouraging to warrant further investigation and trial."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Masuda et al, 1994, Japan[123]	Randomized, double-blind study	30 Patients scheduled for hysterectomy surgery • Lithotomy position (0%, mean 43.7 y ± 6.9) • Supine position (0%, mean 37.1 y ± 10.0)	Intrathecal tetracaine with patients placed in either the • Lithotomy position (15) or • Supine position (15)	Arterial pressure, heart rate, cardiac output, cephalad spread of analgesia	"The lithotomy position employed in spinal anesthesia with a hyperbaric solution has no effect on the anesthetic level and hemodynamics."
McClure et al, 1982, UK[124] Wildsmith et al, 1982[167]	–	40 Patients scheduled for surgery on the legs or perineum • Group A (gender not specified, mean 45 y ± 15) • Group B (gender not specified, mean 40 y ± 13) • Group C (gender not specified, mean 36 y ± 15) • Group D (gender not specified, mean 42 y ± 12)	Intrathecal tetracaine administered at a specific volume and rate: • Group A: 1 mL at 1 mL/5 seconds (10) • Group B: 2 mL at 1 mL/5 seconds (10) • Group C: 4 mL at 1 mL/5 seconds (10) • Group D: 4 mL at 1 mL/10 seconds (10)	Level of anesthesia, motor block, duration of anesthesia	"We conclude that isobaric local anaesthetic solutions should be of sufficient concentration to allow an adequate dose to be given in a low volume. In this study we have shown that blockade resulting from the use of low volume isobaric solutions is predictable and limited to the legs and perineum and has minimal effects on the circulation."
Moore et al, 1980, US[54]	Randomized, double-blind study	435 Patients undergoing operations on the lower extremity or perineum or intra-abdominal gynecologic surgery (gender and age not specified)	Intrathecal administration of either: • Bupivacaine 7.5 mg (120) • Tetracaine 6-8 mg (95) • Bupivacaine 12 mg (42) • Tetracaine 10-15 mg (42) • Bupivacaine 12 mg with epinephrine (43) • Tetracaine 10-15 mg with epinephrine (44)	Onset and maximum dermatome level of sensory anesthesia	"Bupivacaine 0.75% in 8.25% dextrose is a safe, reliable local anesthetic solution for spinal anesthesia."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Moore et al, 1968, US[125]	–	19,672 Patients undergoing surgical or obstetric procedures (gender and age not specified)	Epidural block (7286) or spinal anesthesia (12,386) with 1 of the following: • Tetracaine-dextrose and epinephrine (7010) • Tetracaine-dextrose and phenylephrine (1868) • Tetracaine-dextrose and ephedrine (85) • Tetracaine-dextrose (2367) • Tetracaine and epinephrine (211) • Tetracaine and phenylephrine (192) • Tetracaine and ephedrine (1) • Tetracaine (173) • Dibucaine and epinephrine (1) • Dibucaine (441) • Procaine (25) • Piperocaine (12)	Duration of analgesia	"A study of 12,386 spinal blocks and 7286 epidural blocks revealed: (1) both technics to be safe, provided the physician administering the block carefully evaluates his own capabilities and the patient's physical status; (2) spinal block to be the more certain of the two procedures; and (3) the complications and the hazards of the two technics to be similar."
Munoz et al, 1992, Chile[126]	Prospective, double-blind, and randomized study	80 Patients scheduled for elective surgery • No premedication (85%, mean 75 y ± 5) • Flunitrazepam (85%, mean 74 y ± 5) • Lorazepam (95%, mean 73 y ± 4) • Midazolam (85%, mean 73 y ± 5)	Intrathecal administration of lidocaine and/or tetracaine plus 1 of the following: • No premedication (20) • Flunitrazepam (20) • Lorazepam (20) • Midazolam (20)	Incidence of hypoxemia	"In conclusion, premedication with benzodiazepines in geriatric patients was associated with an increased incidence of hypoxemia. Although easily treated, these episodes of desaturation may be potentially life-threatening if undetected. Drowsy patients and those with a higher anesthetic level during surgery were especially susceptible. We believe that in this population the use of a pulse oximeter and/or oxygen administration should be obligatory."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Nakagawa et al, 2000, Japan[127]	Prospective, randomized, controlled and single-blind study	50 Patients undergoing elective gynecological laparotomy • Control (0%, mean 47.7 y ± 8.7) • Midazolam (0%, mean 46.3 y ± 9.9)	Intrathecal tetracaine plus premedication with either • Control (25) or • Midazolam (25)	Level of sedation	"In conclusion, midazolam premedication reduces propofol requirements for sedation, increases the incidence of intraoperative amnesia, and has no effect on the incidence of other complications. Thus, midazolam premedication is helpful as a sedation adjunct to spinal anesthesia using with propofol."
Naulty et al, 1990, US[64]	–	2511 Patients undergoing cesarean delivery (0%, age not specified)	Spinal anesthesia with 1 of the following: • Tetracaine-procaine (804) • Bupivacaine-glucose (942) • Lidocaine-glucose (765)	Incidence of postdural puncture headache	"Further studies should be performed to confirm or deny the validity of our admittedly preliminary observations."
Okutomi et al, 1998, Japan[128]	–	42 Patients undergoing arthroscopy of the knee (60%, range 17-57 y)	Intrathecal tetracaine in either: • Glucose 10% (9) • Sodium chloride 5% (9) • Glucose 5% (12) • Sodium chloride 2.5% (12)	Level of sensory block	"The present study did not clarify the reason behind the relatively more extensive spread of the more viscous solution. We suggest that a high viscosity may indicate poor diffusibility, so that its viscous gradient in the CSF [cerebrospinal fluid] may induce a more extensive spread of the anaesthetic. In contrast, a solution of low viscosity may diffuse into the CSF in a few minutes, being in equilibrium with the CSF, and thus leading to a less extensive spread of the anaesthetic."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Olsfanger et al, 1999, Israel[65]	Prospective, randomized, open-label study	21 Patients undergoing transurethral prostatectomy (100%, range 56-87 y)	• Intrathecal tetracaine (11) • General anesthesia (10)	Intraabdominal pressure, bladder compliance	"In summary, we found that spinal anesthesia was associated with a significant increase in bladder compliance. However, following induction of anesthesia, a similar decrease in intraabdominal pressure was recorded in both the spinal and general anesthesia treatment groups. Finally, the influence of these finding on transurethral-related perioperative complications requires further investigation."
Oni et al, 2013, US[66]	–	10 Patients undergoing facial rejuvenation (gender and age not specified)	All patients received benzocaine, lidocaine, tetracaine cream plus either: • Full ablative laser (5) • Fractioned ablative laser (5)	Pain scores	"Data from this study demonstrate that topical anesthetic for facial rejuvenation can be enhanced with laser pretreatment while maintaining safe blood serum levels. Further studies should examine optimal application amount and time to allow safe multipass facial rejuvenation without the need for invasive nerve blocks."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Ota et al, 1994, Japan[130]	–	47 Patients undergoing urologic or gynecologic surgery • Triazolam (23%, mean 49 y ± 14) • Clonidine 75 mcg (17%, mean 52 y ± 16) • Clonidine 150 mcg (17%, mean 49 y ± 13) • Clonidine 300 mcg (40%, mean 53 y ± 12)	Intrathecal tetracaine plus oral administration of 1 of the following: • Triazolam (13) • Clonidine 75 mcg (12) • Clonidine 150 mcg (12) • Clonidine 300 mcg (10)	Sensory block and regression time	"In conclusion, oral clonidine prolongs the duration of tetracaine spinal anesthesia. A dose-response relationship seems to exist with a plateau effect at a dose of 150 mcg. With 300 mcg oral clonidine, compared with 150 mcg clonidine, bradycardia occurred more frequently. Therefore, the optimal dose of oral clonidine which produces a clinically useful prolongation of tetracaine spinal anesthesia without adverse cardiovascular effects appears to be 150 mcg (2.5 mc/kg)."
Ota et al, 1994, Japan[129]	–	40 Patients undergoing urologic surgery (100%, mean 53.4 y ± 12.7)	Intrathecal tetracaine plus oral administration of either: • Triazolam (10) • Clonidine just before spinal anesthesia (10) • Clonidine 1 hour before spinal anesthesia (10) • Clonidine 3 hours before spinal anesthesia (10)	Sensory block	"In conclusion, when administered within 1 h before spinal anesthesia, oral clonidine at a dose of 150 mcg produced a clinically useful enhancement of the duration of tetracaine spinal anesthesia without adverse cardiovascular effects. The prolonging effect of clonidine, however, was not observed when the drug was given 3 h before the anesthesia. This phenomenon suggest that the analgesic effect of clonidine is short-lived and limited in clinical use compared with its hypotensive effect."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Ota et al, 1992, Japan[131]	–	30 Patients undergoing cystoscopy and transurethral prostatic or bladder surgery (100%, mean 49 y ± 15)	Intrathecal tetracaine plus oral administration of either: • Triazolam (10) • Clonidine (10) • Triazolam and intrathecal phenylephrine (10)	Regression of analgesia	"In conclusion, when utilized as premedication 0.15 mg of oral clonidine produced a clinically useful enhancement of the duration of tetracaine spinal anesthesia. When used in conjunction with tetracaine spinal anesthesia, oral clonidine premedication may have a distinct advantage because of its capacity to prolong sensory blockade and its potent sedating properties."
Pan et al, 1994, Taiwan[132]	Single-blind prospective study	156 Patients undergoing cesarean delivery (0%, range 16-40)	Intrathecal tetracaine plus 1 of the following: • Control (23) • Alfentanil 25 mcg (19) • Alfentanil 50 mcg (21) • Alfentanil 100 mcg (20) • Fentanyl 10 mcg (19) • Fentanyl 20 mcg (15) • Sufentanil 5 mcg (15) • Sufentanil 10 mcg (15) • Sufentanil 220 mcg (11)	Onset and duration of sensory block	"In conclusion, sufentanil appears to give better analgesic enhancement that either fentanyl or alfentanil. In addition, the optimal dosage of sufentanil appears to be 10 ug when combined with hyperbaric tetracaine spinal anesthesia without increasing the incidence of adverse effects such as pruritus, nausea, and respiratory depression."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Park et al, 2020, US[55]	Randomized, double-blind, prospective clinical trial	52 Patients undergoing dental procedures (23%, mean 28.1 y ± 4.0)	Topical administration of either: • Benzocaine (26) • Mixture of lidocaine, prilocaine, and tetracaine (26)	VAS scores, changes in heart rate	"The CTA [compound topical anesthetics] mixture showed higher VAS pain scores and caused a significant increase in tissue sloughing at the injection site compared with 20% benzocaine when applied in oral soft tissues after 60 seconds. In this study, no benefits were seen using a CTA of 10% lidocaine, 10% prilocaine, and 4% tetracaine versus 20% benzocaine prior to maxillary infiltration injections."
Park et al, 1975, US[133]	–	222 Patients undergoing operations involving the lower abdomen, perineum, and lower extremities • Control (gender not specified, mean 55.6 y ± 17.3) • Epinephrine (gender not specified, mean 47.8 y ± 15.2) • Phenylephrine (gender not specified, mean 51.8 y ± 15.5)	Intrathecal tetracaine with 1 of the following: • Control (102) • Epinephrine (64) • Phenylephrine (56)	Duration of motor and sensory block	"Neither the differences in overall age, cerebrospinal fluid pH, nor the addition of vasopressors had any significant effect on onset. Duration, however, was significantly prolonged by the addition of vasopressors, 53 percent prolongation by 0.2 mg. of epinephrine and 72 percent prolongation by 2 mg. of phenylephrine."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Penman et al, 1950, US[134]	–	675 Patients receiving labor analgesia (0%, age not specified)	Inhalation anesthesia (100), or spinal administration (575) of either • Ephedrine (75) or • Tetracaine (500)	Sensory anesthetic levels and maximum time the levels were maintained	"In a group of carefully selected patients without complications intrathecally administered ephedrine sulfate solution produced anesthesia satisfactory for delivery in 73 per cent of seventy-five patients. An analysis of this series and a comparison with the results when other agents were used reveal that there is no appreciable decrease in the incidence of maternal or fetal complications. In view of this and the high percentage of failures it is felt that intraspinal ephedrine sulfate solution is of little value for frequent use as an anesthetic agent in obstetrics. However, the results obtained justify continued investigation in an attempt to learn more about its mechanism of action and to determine its range of usefulness in the production of anesthesia."
Peterson et al, 1983, US[135]	Retrospective study	52 Patients who received continuous spinal anesthesia for surgical procedures on the lower extremities or lower abdomen (gender not specified, mean 70 y)	Continuous spinal anesthesia with 1 of the following: • Lidocaine (24) • Hyperbaric tetracaine (15) • Hypobaric tetracaine (2) • Procaine or a mixture of lidocaine, hyperbaric tetracaine, and/or hypobaric tetracaine (11)	Hypotension	"Reports in the literature consistently have shown minimal complications and a wide range of safety with the appropriate use of continuous spinal anesthesia. Our experience has borne this out. We have found the technique to be simple, effective, and safe, particularly for lower abdominal or lower extremity surgery in geriatric patients."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Pflug et al, 1976, US[70]	–	99 Patients undergoing surgical procedures • Tetracaine (100%, mean 59 y ± 2.7) • Bupivacaine (100%, mean 65 y ± 2.1)	Spinal anesthesia with varying doses of either • Tetracaine (50) or • Bupivacaine (49)	Amount of anesthetic agent used, elapsed time for onset of analgesia, elapsed time for obtaining maximum anesthesia	"We conclude that the results obtained with bupivacaine and tetracaine spinal anesthesia are clinically the same (except for an occasional decreased motor block with bupivacaine) when equal hyperbaric doses are used for similar surgical conditions."
Prasad et al, 1989, US[136]	Case report	1 Patient with stage IV vulvar carcinoma admitted for radical vulvectomy and bilateral femoral and pelvic node dissection and a history of intraoral and epiglottic bullae (0%, 49 y)	• Intrathecal tetracaine (1)	Sensory blockade	"In the patient with bullous pemphigoid that we report, regional anesthesia rather than general anesthesia was chosen to prevent oropharyngeal trauma and potential airway obstruction. However, no other precautions were taken to avoid skin or mucous membrane bulla formation, and the patient experienced no significant intraoperative or postoperative exacerbation of her skin disease. Although it is difficult to extrapolate from outcome in one patient, the precautions required in managing patients with epidermolysis bullosa dystrophica may not necessarily be required in patients with bullous pemphigoid."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Rao et al, 1981, US[137]	–	4015 Patients scheduled for lower extremity peripheral vascular surgery (66.1%, mean 61 y)	Subarachnoid block with tetracaine (847), or epidural anesthesia (3164) with 1 of the following: • Lidocaine (594) • Lidocaine plus epinephrine (210) • Mepivacaine (323) • Mepivacaine plus epinephrine (806) • Bupivacaine (607) • Bupivacaine with epinephrine (624)	Incidence of hematomas, neurologic complications, low back pain	"In conclusion, proper patient selection, atraumatic technique, monitoring of anticoagulant activity and removal of the catheter when the circulating heparin level is low should minimize the occurrence of spinal epidural or subarachnoid hematoma following anticoagulant therapy in patients with peridural or subarachnoid catheters."
Rice et al, 1994, US[38]	–	100 Patients scheduled for subdiaphragmatic surgery (gender not specified, range 37 days to 12 months)	Spinal anesthesia with either: • Lidocaine and epinephrine (10) • Tetracaine (22) • Tetracaine and epinephrine (68)	Duration of motor block	"We recommend hyperbaric solutions of lidocaine 3 mg/kg with epinephrine for very brief procedures, tetracaine 0.4 mg/kg for procedures estimated to last 60 minutes, and tetracaine 0.4 mg/kg with epinephrine for procedures estimated to last 90 minutes."
Rocco et al, 1984, US[56]	Double-blind evaluation	60 Patients scheduled for orthopedic surgery • Bupivacaine (43.3%, mean 58.2 y ± [SEM] 2.9) • Tetracaine (53.3%, mean 58.8 y ± [SEM] 2.7)	Intrathecal administration of either • Bupivacaine (30) or • Tetracaine with epinephrine (30)	Frequency of adequate anesthesia; onset and regression of anesthesia; and onset, intensity, and duration of motor block	"The results of this double-blind study suggest that glucose-free bupivacaine may be a useful spinal anesthetic agent for orthopedic surgical procedures of 2 to 4 hours duration."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Rocco et al, 1984, US[57]	Double-blind, randomized study	40 Patients scheduled for extraperitoneal abdominal, perineal, or lower extremity surgery • Bupivacaine (60%, mean 47.8 y ± 4.1) • Tetracaine (65%, mean 46.8 y ± 3.5)	• Intrathecal bupivacaine (20) • Intrathecal tetracaine (20)	Onset and duration of block	"In summary, hyperbaric bupivacaine appears to be a reasonable alternative to tetracaine for the production of spinal surgical anesthesia of 2 to 3 hours duration. Little difference existed between the two agents with regard to onset, spread, and duration of useful sensory analgesia. However, the duration of motor block of the lower limbs was longer following the use of tetracaine. In addition, the frequency of inadequate analgesia may be somewhat less in those patients in whom bupivacaine is employed for spinal anesthesia."
Rocco et al, 1981, US[39]	Double-blind, randomized conditions	30 Patients scheduled for general, orthopedic, or urological surgery (gender and age not specified)	• Intrathecal dibucaine (15) • Intrathecal tetracaine (15)	Level and duration of motor and sensory block	"Hyperbaric 0.25 percent dibucaine and 0.5 percent tetracaine used to produce spinal anesthesia, provided a similar onset, spread and duration of sensory analgesia. However, tetracaine produced more complete sympathetic and motor blockade and showed a tendency to cause more profound sensory anesthesia."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Rooney et al, 1949, US[138]	–	467 Patients undergoing surgery (gender and age not specified)	• Single dose tetracaine (125) • Single dose tetracaine with epinephrine (270) • Fractional dose tetracaine (30) • Fractional dose tetracaine with epinephrine (42)	Duration of analgesia	"1. An epinephrenized syringe technique is presented for prolonging Pontocaine-dextrose spinal analgesia. 2. Clinical data demonstrate that epinephrine administered intrathecally sustains Pontocaine analgesia twenty to seventy minutes beyond that usually given by Pontocaine alone. This represents an average of 35 to 50 per cent increase in the operative time, accomplished with a 10 per cent reduction of Pontocaine dosage. 3. No deleterious effects were noted referrable to the methods in the cases studied."
Rubin et al, 2017, US[139]	–	1 Patient presenting with persistent genital arousal disorder (PGAD) status post–dorsal slit surgery with lysis of clitoral adhesions and removal of keratin pearls (0%, 21 y)	• Topical anesthesia with benzocaine 20%, lidocaine 6%, and tetracaine 6% followed by local injection of lidocaine and bupivacaine before receiving experimental periclitoral injections of botulinum toxin (1)	Resolution of PGAD symptoms	"Peri-clitoral injections with botulinum toxin have provided symptom relief to one woman with PGAD secondary to clitoral small fiber dorsal neuropathy. Botulinum toxin has been shown to exhibit anti-nociceptive properties."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Sakai et al, 2003, Japan[140]	Double-blind prospective study	42 Patients scheduled for TURP • Tetracaine (100%, mean 72 y ± 7.3) • Tetracaine with morphine 0.05 mg (100%, mean 72 y ± 8.4) • Tetracaine with morphine 0.1 mg (100%, mean 72 y ± 7.5)	Intrathecal administration of 1 of the following: • Tetracaine (14) • Tetracaine plus morphine 0.05 mg (13) • Tetracaine plus morphine 0.1 mg (15)	Postoperative pain (VAS), nausea, pruritus	"A dose of 0.05 mg in intrathecal morphine with spinal anesthesia would be optimal for elderly patients undergoing TURP."
Sakura et al, 2001, Japan[141]	–	100 Patients scheduled for elective surgery to the lower limb • Adolescents with tetracaine in glucose (60%, mean 15 y ± 1) • Adolescents with tetracaine in glucose with phenylephrine (60%, mean 16 y ± 1) • Adults with tetracaine in glucose (73%, mean 49 y ± 14) • Adults with tetracaine in glucose with phenylephrine (77%, mean 51 y ± 14)	Adolescent patients with intrathecal tetracaine plus either • Glucose (20) or • Glucose and phenylephrine (20) Adult patients with intrathecal tetracaine plus either • Glucose (30) or • Glucose with phenylephrine (30)	Degree of sensory and motor block	"In conclusion, these results suggest that adolescents develop an extensive level of blockade more easily and quickly than adults after intrathecal hyperbaric tetracaine but that the difference may be reduced by using a less heavy solution."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Sanderson et al, 2014, US[40]	–	4 Patients undergoing rhytidectomy (gender and age not specified)	Each patient had 2 control and 4 treatment sites; additionally, all patients received topical anesthetic containing benzocaine 5% / lidocaine 5% / tetracaine 5% before the procedure and treatment • Control: No hydration (4) • 30 minutes of hydration (4) • 60 minutes of hydration (4)	Thermal damage measure	"These preliminary findings suggest that there is significant clinical benefit in pre-hydration of skin prior to treatment with the PSR [plasma skin regeneration] device for a short period of time, though larger-scale studies may be required to qualify these findings. Nevertheless, the use of topical anesthetic in conjunction with PSR treatments is cost-effective, safe, and simple to implement, making it a valuable component of the care of patients desiring PSR treatment. Further studies with other popular resurfacing devices may be beneficial."
Santos et al, 1984, US[142]	Double-blind fashion	50 Patients scheduled for elective cesarean section • Droperidol (0%, mean 28.6 y ± 7.8) • Normal saline (0%, mean 27.8 y ± 6.8)	• Intrathecal administration of either tetracaine (36) or lidocaine (14) plus intravenous administration of either: • Droperidol (25) • Normal saline (25)	Nausea and vomiting	"Spinal anesthesia (induced with tetracaine or lidocaine) was administered to 50 patients undergoing elective cesarean section. Droperidol (2.5mg) was administered intravenously to 25 of them, the remaining 25 patients received normal saline. All were treated with butorphanol tartrate intravenously after the birth of the infant. Nausea was found significantly less frequently in the droperidol-treated group than in patients given saline."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Schmidt et al, 1988, US[143]	–	50 Patients scheduled for elective transurethral resection of the prostate • Wait before horizontal lithotomy position (100%, mean 69.6 y ± 8.9) • No wait before horizontal lithotomy position (100%, mean 70.2 y ± 7.3)	All patients received spinal anesthesia with tetracaine • Wait (23) • No wait (26)	Blood pressure, heart rate, thoracic sensory level	"In conclusion, we studied 50 patients scheduled for elective TURP under hyperbaric tetracaine spinal anesthesia. There was no statistically significant difference in anesthesia sensory level, blood pressure, or heart rate in patients placed immediately in horizontal lithotomy position compared to patients first kept supine for 10 minutes after receiving the spinal anesthetic. Placing the patient immediately in the horizontal lithotomy position saves operating room time and does not alter the anesthetic course of the patient."
Shin et al, 2011, Korea[144]	Clinical study	60 Patients scheduled to undergo an elective transurethral resection of a bladder tumor • Crystalloid preload group (83%, mean 59.2 y ± 9.6) • Colloid preload group (87%, mean 59.6 y ± 9.8)	All patients received spinal anesthesia with tetracaine with a preload of either • Crystalloid (30) • Colloid (30)	Sensory block level, cerebrospinal fluid movement	"In conclusion, we observed that a crystalloid preload resulted in a rapid increase of CSF [cerebrospinal fluid] production, and we believe that this finding may explain the decreased CSF pulsatile movement in crystalloid preload, in contrast to a preload of colloid, which may be comparable to a no-preload condition. Decreased CSF pulsatile movement in return may be the reason for the delayed time to reach the peak sensory block level in isobaric spinal anesthesia. Therefore, different preload solutions may be a determining factor in the spread of isobaric local anesthetics within the spinal canal."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Shin et al, 2008, Korea[145]	–	68 Patients scheduled to undergo elective transurethral surgery of the bladder • Nonprehydration (71%, mean 57.4 y ± 10.0) • Prehydration (76%, mean 56.0 y ± 10.1) 24 Volunteers undergoing a magnetic resonance image study (100%, mean 28.7 y ± 7.0)	All patients in the clinical spinal anesthesia study received intrathecal tetracaine plus either • Nonprehydration (34) or • Prehydration (34) Infusion of lactated Ringer's solution (24)	Arterial blood pressure, heart rate, sensory block levels, net flow and volume displacement of the CSF	"In conclusion, the rapid administration of crystalloids affects spinal CSF [cerebrospinal fluid] flow and oscillatory motion at the lumbar level, which may contribute to a decrease in the cephalic spread rate of sensory block with isobaric spinal anesthetic drug. Therefore, prehydration may be one of the factors influencing the spread rate of isobaric spinal anesthetic drugs associated with changes in the physical properties of the CSF."
Singh et al, 1994, US[146]	Randomized, double-blind, placebo-controlled protocol	40 Patients undergoing elective lower extremity or urologic procedures • Oral placebo (100%, mean 58.9 y ± 18.9) • Oral placebo and intrathecal fentanyl (100%, mean 56.5 y ± 13.9) • Oral clonidine (100%, mean 66.4 y ± 7.1) • Oral clonidine and intrathecal fentanyl (100%, mean 60.8 y ± 11)	Intrathecal tetracaine plus 1 of the following: • Oral placebo (10) • Oral placebo and intrathecal fentanyl (10) • Oral clonidine (10) • Oral clonidine and intrathecal fentanyl (10)	Level and duration of motor and sensory blocks	"In conclusion, oral clonidine enhanced the onset of sensory block and prolonged the duration of IT tetracaine's sensory and motor block. However, oral clonidine premedication was associated with a higher incidence of hypotensive and bradycardic episodes during spinal anesthesia."
Singh et al, 2013, US[147]	Case series	3 Patients with rhinophyma undergoing ablative fractional photothermolysis (67%, age not specified)	• Topical administration of benzocaine 10% / lidocaine 6% / tetracaine 4% before ablative fractional photothermolysis (3)	Posttreatment complications	"Ablative fractional photothermolysis is a safe, efficacious, and minimally invasive treatment alternative for mild to moderate rhinophyma."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Skretting et al, 1984, Norway[41]	–	40 Patients scheduled for urological surgery (95%, range 50-75 y)	Intrathecal administration of 1 of the following: • Bupivacaine 2 mL (10) • Tetracaine 2 mL (10) • Bupivacaine 3 mL (10) • Tetracaine 3 mL (10)	Spread of analgesia, level and duration of motor blockade	"The drugs produced similar and satisfactory analgesia in the tested concentrations and volumes. Motor blockade was more profound and longer lasting with amethocaine."
Smith et al, 1968, US[42]	–	100 Patients scheduled for elective inguinal herniorrhaphy or transurethral resection of the prostate (gender and age not specified)	• Normal intrathecal tetracaine dose and flexed position (25) • Normal intrathecal tetracaine dose and extended position (25) • Augmented intrathecal tetracaine dose and flexed position (25) • Augmented intrathecal tetracaine dose and extended position (25)	Onset and level of sensory block	"The larger dose produced slightly higher and more prolonged anesthesia. but the difference related to position of the legs remained equally apparent."
Spielman et al, 1984, US[43]	Case report	2 Patients with severe epidermolysis bullosa scheduled for either surgical treatment of vaginal agglutination or establishment of a feeding gastrostomy (50%, range 20-30 y)	• Intrathecal tetracaine (1) • Epidural 2-chloroprocaine (1)	Successful anesthesia	"In conclusion, we have employed subarachnoid and epidural blockade in two EB [epidermolysis bullosa] patients, with excellent patient acceptance, and have observed no complications. The use of regional anaesthesia avoids the potentially serious complication of air-way manipulation in these patients."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Stevens et al, 1997, US[148]	Randomized, double-blind	12 Volunteers undergoing spinal anesthesia (83.33%, mean 37 y ± 1)	• Intrathecal administration of equipotent doses of tetracaine, bupivacaine, and lidocaine (12)	Level of analgesia, cold pressor test	"Spinal anesthesia with hyperbaric solutions of tetracaine 15 mg, bupivacaine 15 mg, and lidocaine 100 mg attenuated sympathetic function but did not produce complete sympathectomy. The effects were independent of the local anesthetic used."
Sumi et al, 1998, Japan[149]	–	91 Patients scheduled for elective surgery to the lower limb (53.8%, range 14-77 y)	Intrathecal tetracaine with phenylephrine before being placed: • Supine immediately after spinal injection (30) • Lateral position for 10 minutes before turning supine (30) • Lateral position for 20 minutes before turning supine (31)	Neural block, hemodynamic variables	"The effects of posture on the spread of hyperbaric spinal anesthesia have not been adequately investigated. The results of the present study suggest an advantage of prolonged lateral decubitus positioning after intrathecal hyperbaric tetracaine."
Sumi et al, 1996, Japan[150]	–	120 Patients scheduled for elective surgery to the lower limb • Tetracaine in glucose 7.5% (43%, mean 49 y ± 3) • Tetracaine in glucose 0.75% (63%, mean 45 y ± 4) • Tetracaine in glucose 7.5% and phenylephrine (47%, mean 50 y ± 3) • Tetracaine in 0.75% glucose and phenylephrine (57%, mean 49 y ± 4)	Intrathecal administration of either: • Tetracaine in glucose 7.5% (30) • Tetracaine in glucose 0.75% (30) • Tetracaine in glucose 7.5% and phenylephrine (30) • Tetracaine in 0.75% glucose and phenylephrine (30)	Level and degree of sensory and motor block	"In conclusion, tetracaine 0.5% in glucose 0.75% with or without phenylephrine 0.125%, which is marginally hyperbaric, can produce consistent blocks with spread restricted to the lower thoracic segments causing less haemodynamic variability when administered intrathecally at the L3-4 interspace with a patient in the lateral position."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Tan et al, 2000, China[151]	Randomized, double-blind	60 Patients scheduled for elective inguinal herniorrhaphy • Tetracaine (100%, mean 21.9 y ± SEM 0.7) • Tetracaine with neostigmine 50 mcg (100%, mean 21.8 y ± SEM 2.2) • Tetracaine with neostigmine 100 mcg (100%, mean 23.6 y ± SEM 9.9)	Intrathecal administration of 1 of the following: • Tetracaine (20) • Tetracaine with neostigmine 50 mcg (20) • Tetracaine with neostigmine 100 mcg (20)	Onset of anesthesia, duration of analgesia, time to first rescue analgesic, overall VAS pain scores, incidence of adverse effects	"Our study showed that intrathecal neostigmine at 50 mcg or 100 mcg enhanced the onset of tetracaine anaesthesia and provided analgesia lasting for 6-9 h, although increased incidences of prolonged motor blockade and nausea or vomiting were noted."
Tan et al, 2001, Taiwan[152]	Randomized, double-blind, placebo-controlled protocol	60 Patients posted for elective inguinal herniorrhaphy • Placebo (100%, mean 23.7 y ± SEM 2.3) • Dexamethasone (100%, mean 22.3 y ± SEM 2.4)	Intrathecal tetracaine with neostigmine plus intravenous administration of either • Placebo (30) or • Dexamethasone (30)	Duration of absolute anesthesia, time of first rescue analgesia, VAS pain scores, motor block duration	"We found that prophylactic administration of IV dexamethasone 10 mg did not enhance the analgesia or reduce the incidence of emesis in patients receiving spinal anesthesia with tetracaine plus neostigmine 100 mg during inguinal herniorrhaphy."
Tsai et al, 1985, Taiwan[153]	Single-blind, randomized fashion	80 Patients posted for transurethral prostrate resection • Tetracaine (100%, mean 65 y) • Tetracaine with butorphanol (100%, mean 64 y)	Spinal anesthesia with either • Tetracaine and adrenaline (45) or • Tetracaine, adrenaline, and butorphanol (35)	Sensory and motor block	"We conclude that the lack of adverse effects associated with intrathecal butorphanol makes it a usable alternative to morphine for the relief of postoperative pain."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Uchiyama et al, 1994, Japan[154]	Double-blind fashion	80 Patients scheduled for elective cesarean delivery • Control (0%, mean 32.2 y ± SEM 5.8) • Morphine 005 mg (0%, mean 31.5 y ± SEM 5.4) • Morphine 0.1 mg (0%, mean 31.3 y ± SEM 5.6) • Morphine 0.2 mg (0%, mean 28.7 y ± SEM 4.8)	Intrathecal tetracaine plus either: • Control (20) • Morphine 0.05 mg (20) • Morphine 0.1 mg (20) • Morphine 0.2 mg (20)	Need for rescue analgesia, side effects	"Intrathecal morphine doses of 0.1 and 0.2 mg are equally effective for pain relief after caesarean section. Since 0.1 mg results in fewer and less serious postoperative side-effects, it appears to be the appropriate supplement for intrathecal local anesthetic solutions."
Urban et al, 1973, US[155]	–	14 Patients undergoing elective operations (71%, age not specified)	• Spinal anesthesia with tetracaine and epinephrine (9) • Epidural anesthesia with lidocaine and epinephrine (4) • Epidural anesthesia with mepivacaine and epinephrine (1)	Cranial borders of analgesia	"It is suggested that local anesthetics act first upon radicular structures and later upon structures inside the spinal cord. Because of different rates of anesthetic uptake and elimination, cord blockade becomes clinically apparent after the block of the more peripheral structures has worn off."
Van Gessel et al, 1989, Switzerland[71]	–	30 Patients undergoing surgical repair of hip fractures • Tetracaine (13.3%, mean 86 y ± 2) • Bupivacaine (13.3%, mean 84 y ± 1)	Spinal anesthesia with either: • Tetracaine (15) • Bupivacaine (15)	Sensory levels, duration of analgesia	"The authors conclude that hyperbaric solutions of both tetracaine and bupivacaine are suitable for surgical repair of hip fractures in geriatric patients and produce comparable anesthetic and hemodynamic effects."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Van Gessel et al, 1992, Switzerland[72]	Double-blind and randomized fashion	30 Patients scheduled for elective total hip replacement • Tetracaine (13.3%, mean 80 y ± 5) • Bupivacaine (13.3%, mean 80 y ± 5)	Spinal anesthesia with either • Tetracaine (15) or • Bupivacaine (15)	Sensory level, duration of analgesia	"The authors conclude that, during continuous spinal anaesthesia, equipotent hyperbaric solutions of bupivacaine and tetracaine have similar anaesthetic and haemodynamic effects."
Viscomi et al, 1995, US[67]	–	14 Patients presenting for meningomyelocele closure (71%, mean 38 weeks ± 1.5)	• Spinal anesthesia with tetracaine and epinephrine (14)	Blood pressure, heart rate, oxyhemoglobin saturation	"In summary, the use of spinal anesthesia was a safe and effective technique in our series of neonates requiring meningomyelocele closure. Postoperative respiratory monitoring remains essential, particularly if intraoperative sedatives are administered. Conservative initial tetracaine doses can be chosen, since additional subarachnoid injections can be performed intraoperatively if necessary. Studies comparing respiratory and neurologic outcomes between neonates receiving spinal or general anesthesia for meningomyelocele closure appear to be warranted."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Wang et al, 2020, China[44]	Randomized, double-blind, active comparator trial	523 Patients who required diagnosis and treatment using bronchoscopy • Tetracaine pure solution aerosol inhalation (63%, mean 54.94 y ± 15.27) • Diluted tetracaine aerosol inhalation (62%, mean 56.68 y ± 15.81)	Oral dyclonine hydrochloride plus • Tetracaine pure solution aerosol inhalation (262) or • Diluted tetracaine aerosol inhalation (261)	Anesthetic effect, adverse reactions	"In conclusion, we found that 1% tetracaine hydrochloride injection pure liquid atomization inhalation combined with oral administration of dyclonine hydrochloride mucilage for local anesthesia of upper respiratory tract for bronchoscopy had a better anesthesia effect. It can improve the patient's tolerance; reduced the discomfort caused by nose, epiglottis and vocal cord contact, stimulation and friction during bronchoscopy; and reduced complications, such as hypoxia and nausea, etc. This method is simple, feasible, easily accepted by patients, safe to use and has fewer side effects. Furthermore, it has a good anesthetic effect and warrants clinical application."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Welborn et al, 1990, US[156]	–	36 Patients undergoing anesthesia for inguinal hernia repair • General anesthesia (gender not specified, mean 43.3 weeks ± 3.9) • Spinal anesthesia and ketamine (gender not specified, mean 41.2 weeks ± 2.9) • Spinal anesthesia (gender not specified, mean 40.5 weeks ± 3.4)	• General anesthesia (16) • Intrathecal tetracaine and epinephrine plus intramuscular ketamine (9) • Intrathecal tetracaine and epinephrine (11)	Postoperative apnea	"In summary, this study shows that spinal anesthesia without ketamine sedation was not associated with postoperative apnea, whereas infants receiving either general anesthesia or spinal anesthesia plus ketamine sedation experienced a 31% and 89% incidence of postoperative apnea, respectively. Because of the small number of infants examined in this series and the multiple factors that may influence the incidence of postoperative apnea (e.g., prior history of neonatal apnea) we believe that it is prudent to continue cardiorespiratory monitoring for at least 12 h postoperatively in all high-risk infants who are younger than 44-46 weeks postconceptual age following all anesthetic techniques."
Werner et al, 1982, Australia[157]	Double-blind trial	190 Patients undergoing upper gastrointestinal endoscopy • Phenoperidine (63%, mean 53.1 y ± 16.1) • Diazepam (65%, mean 51.3 y ± 16.1)	Intravenous atropine and tetracaine throat spray plus either: • Oral diazepam (95) • Oral Phenoperidine (95)	Ease of intubation, patient discomfort	"This study clearly demonstrates that intravenous phenoperidine (2 mg) is a very satisfactory premedication for upper gastrointestinal endoscopy as judged by the endoscopist and patient. In addition phenoperidine has the distinct advantage over diazepam as its effect on the respiratory system is rapidly reversible by the use of intravenous naloxone hydrochloride."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Wildsmith et al, 1981, UK[158]	–	30 Patients undergoing surgery to the legs or perineum (gender and age not specified)	Intrathecal tetracaine dissolved in varying volumes of saline: • 1 mL (10) • 2 mL (10) • 4 mL (10)	Level and duration of analgesia	"These results confirm our earlier finding that, in the range used clinically, volume has little effect on the spread of solutions injected intrathecally. Four millilitre is a relatively large volume and yet the main effect was to increase the unpredictability of the blocks. We would infer that barbotage, which is really one way of increasing the volume of an injected solution, may have the same undesirable effect."
Williams et al, 1997, US[24]	Case report/institutional review	1 Patient diagnosed with mild respiratory distress syndrome undergoing laparotomy with a diagnosis of small bowel obstruction (0%, 29 weeks) 19 Patients who had undergone major abdominal surgeries (gender not specified, range 1 day - 7 months)	• Intrathecal tetracaine with epinephrine (1) • Intrathecal tetracaine (19)	Need for intraoperative and postoperative supplements	"Although this series is not a controlled trial of the benefits of general vs regional anaesthesia in neonates, several observations are possible. It demonstrates the feasibility of utilizing a purely regional anaesthetic technique in small infants for procedures more complicated than has been used previously. Normally, several of the infants in this series would have required postoperative ventilation and/or postoperative opioids. If postoperative ventilation can be avoided or minimized in these high risk infants, the potential for decreased morbidity and considerable cost savings may be significant. Complications associated with the technique have been minimal. A randomized controlled trial would be of benefit to explore further the potential benefits of this approach."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Yamakage et al, 1999, Japan[159]	Randomized, placebo-controlled study	40 Patients undergoing surgery on the lower abdomen or a lower extremity • Propofol (60%, mean 59 y ± 12) • Midazolam (53.3%, mean 56 y ± 8) • Placebo (60%, mean 54 y ± 8)	Spinal anesthesia with tetracaine along with sedation provided intravenously by 1 of the following: • Propofol (15) • Midazolam (15) • Placebo (10)	Changes in respiratory pattern and arterial blood gases	"Spinal anesthesia per se increased the rib cage contribution to the tidal volume (%RC) without changing any other respiratory parameters. Sedation with propofol and midazolam during spinal anesthesia substantially decreased %RC with respiratory depression, and the effect of propofol was greater. Because this difference seems to depend on paradoxical respiration due to upper airway obstruction, attention should be directed to the respiratory pattern during sedation, especially during sedation with propofol."
Yanagidate et al, 2001, Japan[160]	Randomized, double-blinded manner	46 Patients undergoing cesarean delivery • Atropine and famotidine with clonidine (0%, mean 29 y ± 5) • Atropine and famotidine (0%, mean 28 y ± 4)	Intrathecal tetracaine plus oral administration of either • Atropine, famotidine, and clonidine (23); or • Atropine and famotidine (23)	Hemodynamic instability, VAS scores, APGAR scores	"The present results indicate that oral clonidine reduces the PCA [patient-controlled analgesia] morphine requirement after C-section without compromising the condition of the fetus or newborn. Further study including larger number of patients would be needed before we conclude that oral clonidine for parturients is safe for their newborns."
Yang et al, 2007, Korea[161]	–	36 Patients undergoing varicose vein surgery • Hyperbaric tetracaine (55.5%, mean 46.2 y) • Isobaric tetracaine (61.1%, mean 46.6 y)	Intrathecal administration of either • Hyperbaric tetracaine (18) or • Isobaric tetracaine (18)	Propofol requirement for sedation	"The known difference in level of spinal anaesthetic block induced by solutions of different baricity, but the same dose of local anaesthetic, was associated with different requirements for propofol sedation as determined by BIS assessment."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (No. of patients)	Primary Outcome Measure	Authors' Conclusions
Yotsui et al, 2004, Japan[162]	–	20 Patients undergoing urological, orthopedic, or vascular surgery • Control (50%, mean 48.7 y ± 11.6) • Epinephrine (50%, mean 50.7 y ± 20.1)	Intrathecal tetracaine plus either • Control (10) or • Epinephrine (10)	BIS score	"Intrathecal epinephrine augments the sedative effect of propofol during spinal anesthesia."

Abbreviations: "–", not mentioned; APGAR, appearance, pulse, grimace, activity, and respiration; BIS, bispectral index; BLT, Benzocaine/lidocaine/tetracaine; CSF, cerebrospinal fluid; PGAD, persistent genital arousal disorder; TURP, transurethral resection of the prostate; US, United States; VAS, visual analog scale.
[a]As defined by authors.

Appendix 3.1. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you prescribe or administer tetracaine hydrochloride to your patients?
    - Yes
    - No
3. Do you prescribe or administer tetracaine hydrochloride by any of the following dosage forms and/or routes of administration? (check all that apply)
    - Intrathecal injectable solution
    - Nasal liquid products
    - Oral products
    - Topical products including but not limited to cream, emulsion, gel, ointment, solution, suspension
    - None of the above
4. I prescribe or administer tetracaine hydrochloride for the following conditions or diseases: (check all that apply)
    - Anesthesia
    - Dental numbing agent
    - Pain
    - Other (please explain) _____
5. I prescribe or administer tetracaine hydrochloride in combination with other active pharmaceutical ingredients as a multi-ingredient product.
    - Yes
    - No
6. I prescribe or administer tetracaine hydrochloride with my patients as the following: (check all that apply)
    - FDA-approved drug product
    - Compounded drug product
    - Other (please explain)
7. I use compounded tetracaine hydrochloride because: (check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
    - Patient allergies prevent me from using commercially available products (please explain) _____

- Patient conditions prevent me from using commercially available products (please explain) _____
- I am not aware of any commercially available products containing tetracaine hydrochloride
- Other (please explain) _____

8. Do you stock non-patient-specific compounded tetracaine hydrochloride at your practice?
   - Yes
   - No
   - I'm not sure
9. I obtain compounded tetracaine hydrochloride from the following: (check all that apply)
   - Compound myself at my practice
   - Have the product compounded by an in-house pharmacy
   - Purchase, or have a patient purchase, from a compounding pharmacy
   - Purchase, or have a patient purchase, from an outsourcing facility
   - Other (please explain) _____
10. What is your practice setting? (check all that apply)
    - Physician office/private practice
    - Outpatient clinic
    - Hospital/health system
    - Academic medical center
    - Emergency room
    - Operating room
    - Other (please describe) _____
11. What degree do you hold? (check all that apply)
    - Doctor of Medicine (MD)
    - Doctor of Osteopathic Medicine (DO)
    - Doctor of Medicine in Dentistry (DMD/DDS)
    - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - Naturopathic Doctor (ND)
    - Nurse Practitioner (NP)
    - Physician Assistant (PA)
    - Other (please describe) _____

Appendix 3.2. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Which of the following drugs do you prescribe or administer to your patients? (please check all that apply)
    - ○ Acetylcysteine
    - ○ Bupivacaine hydrochloride
    - ○ Clonidine hydrochloride
    - ○ Tetracaine hydrochloride
    - ○ Triamcinolone acetonide
    - ○ Tropicamide
    - ○ None of the above
3. I prescribe or administer compounded [substance from question 2] in combination with other active pharmaceutical ingredients as a multi-ingredient product.
    - ○ Yes, please explain _____
    - ○ No
4. Do you prescribe or administer [substance from question 2] by any of the following dosage forms and/or routes of administration? (please check all that apply)
    a. Local/perineural injection
    b. Intracameral injection
    c. Intraocular injection
    d. Ophthalmic solution, suspension, or gel
    e. Other (please describe) _____
    f. None of the above
5. I prescribe or administer [substance from question 2] for the following conditions or diseases:
    a. Anesthesia for ophthalmic procedures
    b. Dilation for mydriasis induction
    c. Dry eye caused by meibomian gland dysfunction
    d. Peribulbar or retrobulbar block
    e. Other, please explain _____
    f. None of the above
6. I prescribe or administer [substance from question 2] with my patients as the following;
    a. FDA-approved drug product
    b. Compounded drug product

c. Over-the-counter drug product
d. Other (please explain) _____

7. I used compounded [substance from question 2] because: (please check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
    - Patient allergies prevent me from using commercially available products (please explain) _____
    - Patient conditions prevent me from using commercially available products (please explain) _____
    - I am not aware of any commercially available products containing [substance from question 2]
    - Other (please explain) _____
8. Do you stock non-patient-specific compounded [substance from question 2] at your practice?
    - Yes
    - No
    - I'm not sure
9. I obtain compounded [substance from question 2] from the following: (please check all that apply)
    - Compound myself at my practice
    - Have the product compounded by an in-house pharmacy
    - Purchase, or have a patient purchase, from a compounding pharmacy
    - Purchase, or have a patient purchase, from an outsourcing facility
    - Other (please explain) _____
10. What is your practice setting? (please check all that apply)
    - Physician office/private practice
    - Outpatient clinic
    - Hospital/health system
    - Academic medical center
    - Emergency room
    - Operating room
    - Other (please describe) _____
11. What degree do you hold? (please check all that apply)
    - Doctor of Medicine (MD)
    - Doctor of Osteopathic Medicine (DO)
    - Doctor of Medicine in Dentistry (DMD/DDS)
    - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - Naturopathic Doctor (ND)
    - Nurse Practitioner (NP)
    - Physician Assistant (PA)
    - Other (please describe) _____

Appendix 3.3. Survey instrument for professional medical associations

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	○	○	○
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	○	○	○
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	○	○	○

2. Do you prescribe or administer any of the following as a compounded topical product? (please check all that apply)
    - ○ Betamethasone acetate
    - ○ Betamethasone dipropionate
    - ○ Betamethasone sodium phosphate
    - ○ Cholestyramine resin
    - ○ Cimetidine
    - ○ Clobetasol propionate
    - ○ Clotrimazole
    - ○ Cromolyn sodium
    - ○ Dexamethasone sodium phosphate
    - ○ Diclofenac sodium
    - ○ Finasteride
    - ○ Fluconazole
    - ○ Fluticasone propionate
    - ○ Hydrocortisone
    - ○ Itraconazole
    - ○ Ketoconazole
    - ○ Lidocaine hydrochloride
    - ○ Methylprednisolone acetate
    - ○ Metronidazole
    - ○ Mupirocin
    - ○ Niacinamide
    - ○ Phytonadione (vitamin K1)
    - ○ Prilocaine
    - ○ Spironolactone
    - ○ Sulfacetamide sodium monohydrate
    - ○ Terbinafine hydrochloride
    - ○ Tetracaine hydrochloride
    - ○ Triamcinolone acetonide
    - ○ Zinc oxide

- None of the above

3. Do you prescribe the compounded topical products that you selected in in combination with other active pharmaceutical ingredients as a multi-ingredient product?
    - Yes
    - No
    - I'm not sure
4. Why do you use the compounded topical products that you selected? (please check all that apply)
    - Commercial products are not available in the dosage form, strength, or combination I need (please explain) _____
    - Patient allergies prevent me from using commercially available products (please explain) _____
    - Patient conditions prevent me from using commercially available products (please explain) _____
    - I am not aware of any commercially available products containing these products
    - Other (please explain) _____
5. Do you stock non-patient-specific compounded products at your practice?
    - Yes
    - No
    - I'm not sure
6. I obtain compounded products from the following: (please check all that apply)
    - Compound myself at my practice
    - Have the product compounded by an in-house pharmacy
    - Purchase, or have a patient purchase, from a compounding pharmacy
    - Purchase, or have a patient purchase, from an outsourcing facility
    - Other (please explain) _____
7. What is your practice setting? (please check all that apply)
    - Physician office/private practice
    - Outpatient clinic
    - Hospital/health system
    - Academic medical center
    - Emergency room
    - Operating room
    - Other (please describe) _____
8. What degree do you hold? (please check all that apply)
    - Doctor of Medicine (MD)
    - Doctor of Osteopathic Medicine (DO)
    - Doctor of Medicine in Dentistry (DMD/DDS)
    - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - Naturopathic Doctor (ND)
    - Nurse Practitioner (NP)
    - Physician Assistant (PA)
    - Other (please describe) _____

Appendix 3.4. Survey instrument for pharmacy roundtable prequestionnaire

1. Please select all that apply regarding the facility with which you are affiliated.
    - Academic medical center
    - Acute care hospital
    - Children's hospital
    - Community hospital
    - Critical access hospital
    - Dialysis center
    - Federal government hospital
    - Health system
    - Inpatient rehabilitation center
    - Long-term acute care hospital
    - Outpatient surgery center
    - Rural hospital
    - Skilled nursing facility
    - Specialty hospital, please identify specialty(ies)
    - Trauma center
    - Urban hospital
2. Please select the number of beds in the facility with which you are affiliated.
    - < 50
    - 50-99
    - 100-199
    - 200-299
    - 300-399
    - 400-599
    - > 600
3. Do you use an outsourcing facility (503b facility) to obtain any products used in your facility? A list of FDA registered outsourcing facilities can be found at https://www.fda.gov/drugs/human-drug-compounding/registered-outsourcing-facilities.
    - Yes
    - No
4. Why do you use an outsourcing facility to obtain product(s)? Please select all that apply
    - Backorders
    - Convenience
    - Cost
    - Need for concentrations not commercially available
    - Need for preservative-free products
    - Need for ready-to-use products
    - No FDA-approved products available
    - No onsite compounding facility
    - Onsite compounding facility not equipped to compound all necessary products
    - Other, please explain _____
5. Please select the type(s) of products obtained from an outsourcing facility.
    - Nonsterile products
    - Sterile products
6. Please select the category(ies) of products obtained from an outsourcing facility.
    - Cardioplegic solutions
    - Dermatologic preparations
    - Dialysate solutions

- Fluids
- Ophthalmic preparations
- Patient-controlled analgesia
- Ready-to-use anesthesia syringes
- Ready-to-use antibiotic syringes and/or bags
- Ready-to-use electrolyte solutions
- Ready-to-use vasopressor solutions
- Total parenteral nutrition solutions
- Other, please identify _____

7. From the list below, please select the drug(s) that you obtain as either a single ingredient or multi-ingredient product from an outsourcing facility.
    - Acetylcysteine
    - Adenosine
    - Aluminum potassium sulfate
    - Aspartic acid
    - Atenolol
    - Atropine
    - Baclofen
    - Betamethasone
    - Biotin
    - Bupivacaine
    - Calcium chloride
    - Caffeine sodium benzoate
    - Cholecalciferol
    - Chromium chloride
    - Clonidine
    - Dexamethasone sodium phosphate
    - Diclofenac
    - Gentamicin
    - Glycerin
    - Hydroxyzine
    - Ketamine
    - Levocarnitine
    - Lidocaine
    - Lorazepam
    - Magnesium sulfate
    - Manganese chloride
    - Methylprednisolone
    - Midazolam
    - Mupirocin
    - Norepinephrine
    - Ondansetron
    - Phytonadione
    - Potassium chloride
    - Potassium phosphate
    - Prilocaine
    - Proline
    - Propranolol
    - Ropivacaine
    - Sodium chloride
    - Sodium citrate

- Sodium phosphate
- Tetracaine
- Triamcinolone acetonide
- Tropicamide
- None of the above

Appendix 4. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Anesthesiology	Society of Cardiovascular Anesthesiologists	Declined – failed to respond
Cardiology	American Academy of Cardiovascular Perfusion	Declined
	American Board of Cardiovascular Perfusion	Declined – failed to respond
	American Society of Extracorporeal Technology	Declined – failed to respond
Dermatology	American Academy of Dermatology	Declined – failed to respond
Naturopathy	American Association of Naturopathic Physicians	Agreed
Nephrology	American Society of Diagnostic and Interventional Nephrology	Declined
Ophthalmology	American Academy of Ophthalmology	Declined – failed to respond
	American Society of Cataract and Refractive Surgery	Agreed
	American Society of Retina Specialists	Declined
Podiatry	American Podiatric Medical Association	Agreed
Psychiatry	The International Society for Electroconvulsive Therapy and Neurostimulation	Agreed
Rheumatology	American College of Rheumatology	Agreed
Surgery	American Association of Neurological Surgeons	Declined – failed to respond
	American Association for Thoracic Surgery	Declined – failed to respond
	American College of Surgeons	Declined – failed to respond
	American Society for Reconstructive Microsurgery	Declined – failed to respond
Urology	Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction	Declined
Wound Care	Association for the Advancement of Wound Care	Declined – failed to respond

[a]Associations that declined in Year 1 and/or Year 2 were not contacted in Year 3.