Received: 11 January 2024 | Accepted: 26 March 2024

DOI: 10.1002/prp2.1196

ORIGINAL ARTICLE

Absorption and pharmacokinetics of bupivacaine after bilateral topical administration in tonsillar fossae for posttonsillectomy pain relief

Kristin Sandal Berg[1,2] | Ellisiv Seines[1] | Peter Gál[1] | Lise Løberg-Emanuelsen[3] | Audun Stubhaug[4,5] | Erik Waage Nielsen[1,2,4,5,6] | Olav Spigset[3,7]

[1]Department of Surgery, Nordland Hospital Trust, Bodø, Norway

[2]Faculty of Nursing and Health Sciences, Nord University, Bodø, Norway

[3]Department of Clinical Pharmacology, St. Olav University Hospital, Trondheim, Norway

[4]Department of Pain Management and Research, Oslo University Hospital, Oslo, Norway

[5]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

[6]Department of Clinical Medicine, Faculty of Health Sciences, UiT the Arctic University of Norway, Tromsø, Norway

[7]Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway

Correspondence
Erik Waage Nielsen, Department of Surgery, Nordland Hospital Trust, Bodø, Norway.
Email: erik.waage.nielsen@gmail.com

Abstract

No previous studies have investigated the systemic absorption of bupivacaine when used topically for posttonsillectomy pain. The present study was undertaken to investigate the pharmacokinetics of bupivacaine after administration by a swab in the tonsillar fossae over 4 min after tonsillectomy. Eleven adult patients undergoing elective tonsillectomy were recruited. After removal of both tonsils, each of the two tonsillar fossae was covered with a swab moistened with 2 mL of bupivacaine 5 mg/mL, that is, a total of 20 mg bupivacaine. Blood samples were drawn after 0, 5, 10, 20, 30, 45, and 60 min. Bupivacaine was analyzed with an ultra-high-performance liquid chromatography–tandem mass spectrometry method. The highest single measured bupivacaine serum concentration was 23.2 ng/mL and took place 10 min after drug administration. Mean (±SD) C_{max} was 11.4 ± 6.0 ng/mL and mean t_{max} was 11.3 ± 4.7 min. Mean $t_{1/2}$ was 31.6 ± 9.3 min. As the toxic concentration threshold has been reported to be in the interval 1500–4500 ng/mL, the concentrations measured were well below 2% of the lowest cited toxic threshold. In conclusion, this study shows that applying 4 mL of bupivacaine 5 mg/mL by a swab in the tonsillar fossae posttonsillectomy yields very low plasma concentrations, suggesting its safe application without any risk of systemic toxic effects.

KEYWORDS
bupivacaine, high-performance liquid chromatography-tandem mass spectrometry, local anesthesia, systemic absorption, tonsillectomy pain

1 | INTRODUCTION

Tonsillectomy is a common surgical procedure, mainly performed in children, adolescents, and young adults. Tonsillectomy is associated with significant postoperative pain. Several studies have suggested that application of local anesthesia immediately after tonsillectomy is associated with reduced postoperative pain the first hours and days after the surgical procedure compared with placebo.[1–3]

Abbreviation: AUC, area under the time–serum concentration curve.

Medium-to-long-acting agents such as bupivacaine,[4] and ropivacaine have been shown to be more effective than short-acting agents such as lidocaine.[1,5] Both topical applications using moistened cotton swabs and tissue infiltration have been used as methods of administration, with similar clinical effects.[3] However, although rare, infiltration anesthesia has been associated with more frequent adverse events than topical administration.[3,6–10] As the toxicity of local anesthetics is closely related to the plasma concentration of the drug,[11] it is of interest to study systemic concentrations of local anesthetic agents when used for posttonsillectomy pain. Systemic intoxication can lead to both central nervous system and cardiovascular symptoms, ranging from mild tingling and dizziness to severe cardiac arrhythmias or seizures. The critical plasma concentration is typically considered to be around 2–4 μg/mL (7–14 μmol/L), beyond which the risk of toxic effects increases substantially. Monitoring these levels ensures patient safety by allowing for the timely management of potential toxicity.

We are not aware of any studies investigating plasma concentrations of bupivacaine when used topically for posttonsillectomy pain. The present study was undertaken to investigate the absorption and pharmacokinetics of bupivacaine after topical administration of 20 mg of bupivacaine over 4 min in the tonsillar fossae after tonsillectomy.

2 | METHODS

The study included 11 adult, healthy patients undergoing elective tonsillectomy at Nordland Hospital, Bodø, Norway. The study was approved by the Regional Committee for Medical and Health Research Ethics in North Norway (REK no. 134665), the Data Protection Officer at Nordland Hospital (Project no. 152), and the Norwegian Medicines Agency (EudraCT no. 2020-002862-15). All included patients received written and oral information about the study and gave their written consent.

All patients underwent standard anesthesia and surgery. The procedure was performed under general anesthesia using propofol and remifentanil and mivacurium. After induction of anesthesia, an arterial cannula was inserted in either the left or right radial artery, and the first blood sample was drawn before the administration of local anesthetic. After both tonsils had been removed, each of the two tonsillar fossae was covered with a cotton swab weighing 1 g dampened with 2 mL of bupivacaine 5 mg/mL each, that is, a total dose of 20 mg. The swabs were applied for 4 min in accordance with a countdown timer on the anesthesia equipment before their removal. Blood samples were drawn at 0, 5, 10, 20, 30, 45, and 60 min after application of the swabs. The arterial cannula was then removed. We did not register any adverse events related to the placement of the arterial cannula or the procedure of the swab application in the tonsillar beds.

The blood sample from the arterial cannula was transferred to serum tubes without gel, the tubes were turned 5–10 times and then left in a rack to coagulate for 30–120 min. The samples were then centrifuged at 2000 × G for 10 min at room temperature. Immediately after centrifugation, serum was transferred to polypropylene tubes and frozen at −80°C until analysis.

2.1 | Analysis of bupivacaine

The analytical method for bupivacaine was based on a method published previously,[12] with some modifications. In brief, at the laboratory, sample preparation was performed using a Hamilton Microlab STAR pipetting robot (Hamilton, Bonaduz, Switzerland). In this study, 100 μL of serum samples/standards/quality controls and 25 μL of the internal standard bupivacaine-d_9 were pipetted onto an Ostro™ 96-well plate (Waters Corp., Milford, MA, USA). Thereafter, protein precipitation was performed by adding 300 μL ice-cold acetonitrile with 1% formic acid. The content in each well was filtrated using a positive pressure processor.

The eluate was analyzed on an Acquity UPLC I-class coupled to a Waters Xevo TQ-S tandem-quadrupole mass spectrometer (Waters Corp., Milford, MA, USA). Chromatographic separation was achieved on an Acquity UPLC HSS T3 (2.1 × 100 mm, 1.8 μm) column with an Acquity UPLC HSS T3 VanGuard precolumn (2.1 × 5 mm, 1.8 μm), using gradient elution with mobile phase consisting of acetonitrile and 0.1% formic acid in water. The total run time was 2.00 min. The Xevo TQ-S was operated in positive electrospray ionization mode with multiple reaction monitoring. Bupivacaine was detected using the mass transitions *m/z* 289.2 >140.1 and *m/z* 289.2 >98.0 for quantification and qualification, respectively. The mass transition *m/z* 298.3 >149.0 was used for detecting bupivacaine-d_9.

The limit of quantification was 5.0 nmol/L (1.4 ng/mL) and the method was linear at least up to 1000 nmol/L (288 ng/mL). Mean recovery was 94.0 ± 4.2%. The intraday and interday coefficients of variation were less than 4.2% at all concentrations tested.

2.2 | Pharmacokinetic analyses

Maximum measured serum concentrations (C_{max}) and the times to achieve these concentrations (t_{max}) were obtained directly from the measured values. Other pharmacokinetic variables were calculated using the pharmacokinetic program package Kinetica, version 4.3 (ThermoFisher Scientific, Waltham, MA, USA). Area under the time–serum concentration curve (AUC) was calculated using a mixed log-linear model with extrapolation to infinity. By applying a noncompartment model, the parameter estimate describing the decrease of the log-concentration (λ_z) was calculated using the best-fit log-linear regression line of the samples representing the elimination phase. The elimination half-life ($t_{1/2}$) was calculated as $\ln 2/\lambda_z$.

3 | RESULTS

Demographic data of the 11 patients and key pharmacokinetic variables are presented in Table 1. Individual time-concentration curves are displayed in Figure 1.

The highest measured bupivacaine serum concentration was 23.2 ng/mL and took place 10 min after drug administration. Mean (±SD) C_{max} was 11.4 ± 6.0 ng/mL and mean t_{max} was 11.3 ± 4.7 min.

TABLE 1 Demographic variables and pharmacokinetic data of bupivacaine after topical administration of 20 mg bupivacaine in the tonsillar fossae for 4 min by a swab in 11 subjects after tonsillectomy.

	Mean ± SD	Min–max
Age (years)	28.6 ± 11.6	17–53
Sex, m/f (*n*)	3/8	–
Body weight (kg)	77.5 ± 16.8	56–112
C_{max} (ng/mL)	11.4 ± 6.0	5.2–22.1
t_{max} (min)	11.3 ± 4.7	5–20
$t_{½}$ (min)	31.3 ± 8.9	15.7–49.5
AUC ([ng/mL] × min)	609 ± 291	323–901

Abbreviations: AUC, area under the time–serum concentration curve; C_{max}, maximum serum concentration; t_{max}, time to achieve maximum serum concentration; $t_{½}$, elimination half-life.

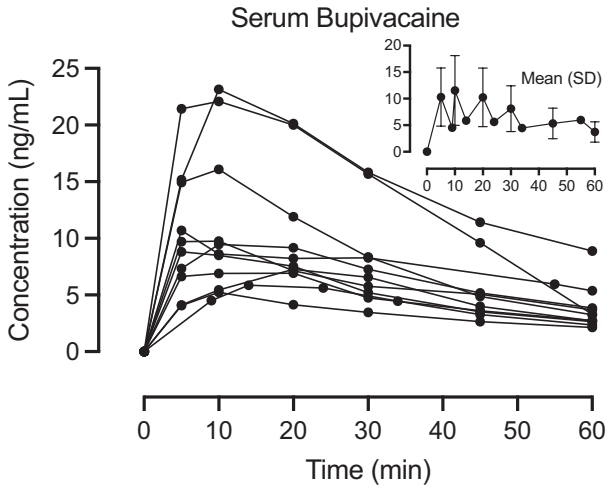

FIGURE 1 Individual bupivacaine serum concentrations (ng/mL) by time (min) in 11 subjects after administration of 4 mL bupivacaine 5 mg/mL in the tonsillar beds by a swab for 4 min after tonsillectomy.

Mean $t_{1/2}$ was 31.6 ± 9.3 min and concentrations after 60 min varied between 2.2 and 8.9 ng/mL.

No clinical effects suspected to be related to bupivacaine toxicity were observed during anesthesia or during the first 2 h after surgery.

The associations between body weight and C_{max} and between body weight and AUC are presented in Figure 2. None of the correlations were statistically significant.

4 | DISCUSSION

The primary observation of the present study is that the topical administration of 20 mg bupivacaine via dampened cotton swabs within the tonsillar fossae for 4 min yields minimal systemic concentrations of the drug. Various studies cite the toxic concentration threshold of bupivacaine as ranging between 1500 and 4500 ng/mL.[13–16] In our

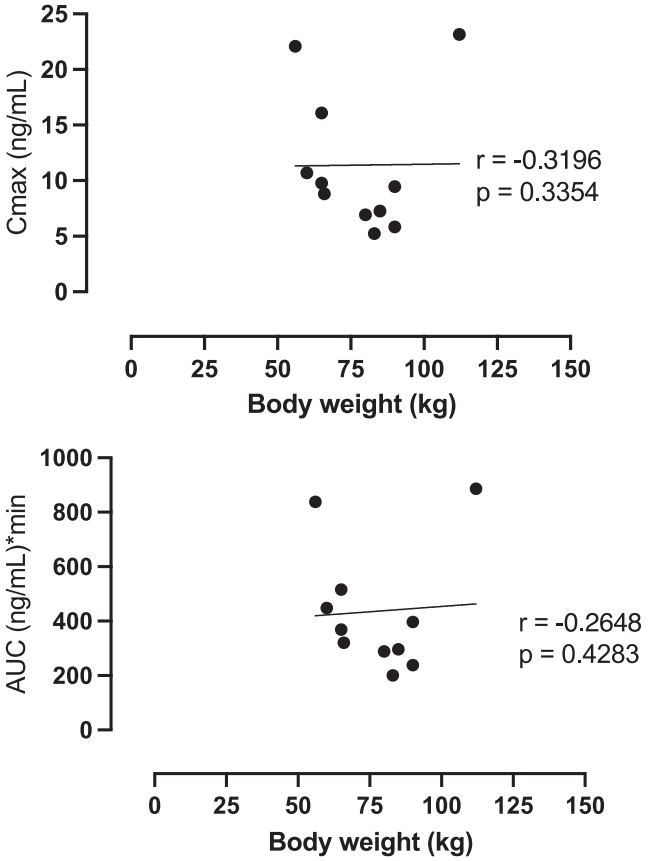

FIGURE 2 Correlations between body weight and maximum serum concentration (C_{max}) for bupivacaine (upper panel) and between body weight and the area under the curve (AUC) for bupivacaine (lower panel).

study, the peak concentration measured was 23.2 ng/mL, which is below 2% of the lowest cited toxic concentration threshold.

Although no previous data exist on the extent of systemic absorption of bupivacaine when used for posttonsillectomy pain management, there are some insights regarding its application within the oral cavity and other parts of the respiratory tract. In an assessment of bupivacaine absorption during fiberoptic bronchoscopy, the average peak concentrations were 271 and 273 ng/mL after application via the upper and lower respiratory tract, respectively.[17] Another investigation, focusing on the absorption of bupivacaine after oropharyngeal spray application in dosages between 20 and 80 mg[18] revealed that even the 20 mg dose yielded a concentration around 150 ng/mL, that is, higher than our findings. A more recent study on the absorption from the oral cavity after lozenge administration of 25 mg of bupivacaine indicated significant absorption variations based on the health of the mucosal membranes.[19] The authors compared the extent of bupivacaine absorption in patients with oral mucositis after radiotherapy with that of healthy individuals and found that the mean plasma concentration in patients with oral mucositis was 2–3-fold higher than in healthy individuals. Moreover, patients with more severe mucositis obtained higher plasma concentrations than patients with milder mucositis. The median plasma concentration among the healthy individuals was just above 200 ng/mL, and

the median plasma concentration among the patients with mucositis was slightly above 400 ng/mL, both substantially higher than the concentrations in the present study.

In our study, peak concentration appeared, on average, 11 min postdrug application, which is faster than the 30–60 min reported in the aforementioned studies.[17–19] This suggests that our 4-min swab application of bupivacaine might have a reduced depot effect post-removal. Obviously, different formulations and application methods could lead to variations in absorption and concentration timelines.

Our study exhibited a fourfold variation in both C_{max} and AUC, potentially due to the varying total areas of the tonsillar beds between subjects. However, other factors like drug loss via swallowing and individual metabolic capacities may also be involved.

Two previous studies asserted the efficacy of topical bupivacaine for posttonsillectomy pain relief.[1,2] These studies employed a slightly higher dose, 5 mL of bupivacaine 5 mg/mL, than in the present study. Our choice of 4 mL of bupivacaine 5 mg/mL was purely practical, driven by the absorption limit of the swabs used.

There are a few limitations to our study. It involved a small sample size of 11 participants, only, and with a brief 60-min blood sampling window. However, such a sample size is not uncommon in pharmacokinetic studies, the degree of extrapolation to calculate AUC to infinity was relatively low at about 30%, and the number of samples in the elimination phase was sufficient to provide robust estimates of elimination half-lives. It could also be considered a limitation that we did not analyze the major bupivacaine metabolites, which could have added depth to our findings. Finally, as the aim of the study was solely pharmacokinetic, we did not register any data related to the extent or duration of the analgesic effect of bupivacaine.

5 | CONCLUSION

This study confirms that applying 4 mL of bupivacaine 5 mg/mL by a swab in the tonsillar fossae posttonsillectomy yields very low plasma concentrations, suggesting its safe application without any risk of systemic toxic effects.

AUTHOR CONTRIBUTIONS

Kristin Sandal Berg, Ellisiv Seines, Peter Gál, and Erik Waage Nielsen have planned and participated in the study, written parts of the manuscript, and reviewed and revised it, providing constructive feedback. Audun Stubhaug has planned, reviewed, revised, and offered constructive comments on the manuscript. Lise Løberg-Emanuelsen has analyzed all the samples, contributed to the manuscript writing, and reviewed and revised it, providing constructive feedback. Olav Spigset designed the experimental setup and perfomed the pharmacokinetic calculations, guided the sample analyses, participated in manuscript writing, and meticulously reviewed and proofread the manuscript in detail. All authors agree to be accountable for all aspects of the work and have approved the final version of the article for submission.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

On demand.

ETHICS STATEMENT

The manuscript adheres to the ethical guidelines as outlined in the author's instructions.

ORCID

Erik Waage Nielsen https://orcid.org/0000-0002-8358-3226
Olav Spigset https://orcid.org/0000-0001-7902-9014

REFERENCES

1. Özmen ÖA, Özmen S. Topical bupivacaine compared to lidocaine with epinephrine for post-tonsillectomy pain relief in children: a randomized controlled study. *Int J Pediatr Otorhinolaryngol*. 2011;75(1):77-80. doi:10.1016/j.ijporl.2010.10.013
2. Haksever M, Özmen S, Akduman D, Solmaz F. Topical bupivacaine compared to bupivacaine infiltration for post-tonsillectomy pain relief in children: a prospective randomized controlled clinical study. *Eur Arch Otorrinolaringol*. 2014;271(9):2555-2559. doi:10.1007/s00405-014-3022-6
3. Grainger J, Saravanappa N. Local anaesthetic for post-tonsillectomy pain: a systematic review and meta-analysis. *Clin Otolaryngol*. 2008;33(5):411-419. doi:10.1111/j.1749-4486.2008.01815.x
4. Harding SD, Sharman JL, Faccenda E, et al. The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. *Nucleic Acids Res*. 2018;46(D1):D1091-D1106. doi:10.1093/nar/gkx1121
5. Ozkiriş M, Kapusuz Z, Saydam L. Comparison of ropivacaine, bupivacaine and lidocaine in the management of post-tonsillectomy pain. *Int J Pediatr Otorhinolaryngol*. 2012;76(12):1831-1834. doi:10.1016/j.ijporl.2012.09.011
6. Bean-Lijewski JD. Glossopharyngeal nerve block for pain relief after pediatric tonsillectomy: retrospective analysis and two cases of life-threatening upper airway obstruction from an interrupted trial. *Anesth Analg*. 1997;84(6):1232-1238. doi:10.1097/00000539-199706000-00011
7. Shlizerman L, Ashkenazi D. Peripheral facial nerve paralysis after peritonsillar infiltration of bupivacaine: a case report. *Am J Otolaryngol*. 2005;26(6):406-407. doi:10.1016/j.amjoto.2005.02.019
8. Weksler N, Nash M, Rozentsveig V, Schwartz JA, Schily M, Gurman GM. Vocal cord paralysis as a consequence of peritonsillar infiltration with bupivacaine. *Acta Anaesthesiol Scand*. 2001;45(8):1042-1044. doi:10.1034/j.1399-6576.2001.450820.x
9. Alsarraf R, Sie KC. Brain stem stroke associated with bupivacaine injection for adenotonsillectomy. *Otolaryngol Head Neck Surg*. 2000;122(4):572-573. doi:10.1067/mhn.2000.104013
10. Fradis M, Goldsher M, David JB, Podoshin L. Life-threatening deep cervical abscess after infiltration of the tonsillar bed for tonsillectomy. *Ear Nose Throat J*. 1998;77(5):418-421.
11. McCaughey W. Adverse effects of local anaesthetics. *Drug Saf*. 1992;7(3):178-189. doi:10.2165/00002018-199207030-00003
12. Larsson M, Sartipy U, Franco-Cereceda A, et al. Extrapleural infusion of levobupivacaine versus levobupivacaine-sufentanil-adrenaline after video-assisted thoracoscopic surgery (VATS): a randomised

controlled trial. *Acta Anaesthesiol Scand*. 2023;67(9):1256-1265. doi:10.1111/aas.14300

13. Scott DB. Evaluation of the toxicity of local anaesthetic agents in man. *Br J Anaesth*. 1975;47(1):56-61. doi:10.1093/bja/47.1.56
14. Munson ES, Tucker WK, Ausinsch B, Malagodi MH. Etidocaine, bupivacaine, and lidocaine seizure thresholds in monkeys. *Anesthesiology*. 1975;42(4):471-478. doi:10.1097/00000542-197504000-00018
15. Tucker GT, Mather LE. Clinical pharmacokinetics of local anaesthetics. *Clin Pharmacokinet*. 1979;4(4):241-278. doi:10.2165/00003088-197904040-00001
16. Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol*. 1998;46(3):245-249. doi:10.1046/j.1365-2125.1998.00775.x
17. McBurney A, Jones DA, Stanley PJ, Ward JW. Absorption of lignocaine and bupivacaine from the respiratory tract during fibreoptic bronchoscopy. *Br J Clin Pharmacol*. 1984;17(1):61-66.
18. Phero JC, Prithvi Raj P, Knarr D, et al. Absorption of bupivacaine after topical application to the oropharynx. *Anesth Prog*. 1987;34(5):187-190.
19. Mogensen S, Sverrisdóttir E, Sveinsdóttir K, et al. Absorption of bupivacaine after administration of a lozenge as topical treatment for pain from oral mucositis. *Basic Clin Pharmacol Toxicol*. 2017;120(1):71-78. doi:10.1111/bcpt.12644

How to cite this article: Berg KS, Seines E, Gál P, et al. Absorption and pharmacokinetics of bupivacaine after bilateral topical administration in tonsillar fossae for posttonsillectomy pain relief. *Pharmacol Res Perspect*. 2024;12:e1196. doi:10.1002/prp2.1196