Article:
Marhofer, P, Columb, M, Hopkins, PM orcid.org/0000-0002-8127-1739 et al. (4 more authors) (2019) Dexamethasone as an adjuvant for peripheral nerve blockade: a randomised, triple-blinded crossover study in volunteers. British Journal of Anaesthesia, 122 (4). pp. 525-531. ISSN 0007-0912

https://doi.org/10.1016/j.bja.2019.01.004

Dexamethasone as an adjuvant for peripheral nerve blockade: A randomized, triple-blinded crossover study in volunteers

P. Marhofer [1] | M. Columb [2] | PM. Hopkins [3] | M. Greher [4] | D. Marhofer [1] | M.R. Levi Bienzle [5] | M. Zeitlinger [5]

[1] Department of Anaesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Vienna, Austria

[2] Department of Anaesthesia, Manchester University Hospitals Foundation Trust; Wythenshawe, United Kingdom

[3] Leeds Institute of Medical Research at St James's, University of Leeds; Leeds, United Kingdom

[4] Department of Anaesthesia, Intensive Care Medicine and Pain Therapy, Herz Jesu Hospital Vienna, Vienna, Austria

[5] Department of Clinical Pharmacology, Medical University Vienna, Vienna, Austria

Correspondence to: Peter Marhofer, MD
Department of Anaesthesia, Intensive Care Medicine and Pain Medicine
Medical University of Vienna
Spitalgasse 21, A-1090 Vienna, Austria
+43 1 40400 41020 (phone)
+43 1 40400 40280 (fax)
(peter.marhofer@meduniwien.ac.at)

Short running title: Dexamethasone for peripheral nerve blockade

MeSH keywords: Dexamethasone (unique ID: D003907); Nerve Block (unique ID: D009407); Anaesthetics, Local (unique ID: D000779); Clinical Study (unique ID: D000068397)

EudraCT: 2018-001221-98

Clinical trial registration number: DRKS 00014604

Abstract

Background

The efficacy of dexamethasone in extending the duration of local anaesthetic block is uncertain. In a randomised controlled triple blind crossover study in volunteers we test the hypothesis that neither intravenous nor perineurally administered dexamethasone prolongs the sensory block achieved with ropivacaine.

Methods

Ultrasound guided ulnar nerve blocks (3 ml ropivacaine 0.75% wt/vol with either 1 ml saline or 4 mg dexamethasone in 1 ml) were performed on three occasions in 24 male volunteers along with a 1 ml IV injection of saline or dexamethasone 4 mg. The combinations of saline and dexamethasone were as follows: *control* group, perineural and IV saline; *perineural* group, perineural dexamethasone and IV saline; *intravenous* group, perineural saline and IV dexamethasone. The sensory block was measured using a visual analogue scale (VAS) in response to pinprick-testing. The duration of sensory block was the primary outcome and time to onset of sensory block the secondary outcome.

Results

All 24 subjects completed the trial. The median (IQR) duration of sensory block was 6.87 (5.85 – 7.62) h in the control group, 7.37 (5.78 – 7.93) h in the perineural group and 7.37 (6.10 – 7.97) h in the intravenous group ($P = 0.61$). There was also no significant difference in the onset time of the blocks between the three groups.

Conclusion

We provide robust evidence that dexamethasone 4 mg has no clinically relevant effect on the duration of sensory block provided by ropivacaine applied to the ulnar nerve.

The ideal agent for peripheral regional anaesthesia would provide sensory and motor block during the surgical procedure followed by prolonged sensory block with return of motor function in the postoperative period. The absence of local anaesthetics with these optimal pharmacodynamic properties has prompted the investigation of drugs that can be administered with local anaesthetics to prolong the duration of peripheral nerve blockade. Dexamethasone, a synthetic corticosteroid and a derivate of hydrocortisone, is currently one of the most interesting and investigated of such adjuvant drugs.

The efficacy of dexamethasone adminstered perineurally or systemically in combination with local anaesthetic peripheral nerve blocks was recently evaluated in seven systematic reviews and meta-analyses with varying results.[1–7] It was suggested that dexamethasone may have a small effect to increase the duration of peripheral regional blocks, but this may apply only when the local anaesthetic solution contains epinephrine. [7] We suggested that the low quality of the trials included in the meta-analyses and the heterogeneity between them (different local anaesthetics, with or without epinephrine, different doses of dexamethasone, different blocks, etc) meant that no reliable conclusion could be drawn regarding the efficacy of perineural dexamethasone in combination with local anaesthetics.[8]

Volunteer studies are well established for investigating the pharmacodynamic characteristics of drugs which can be used for regional anaesthetic purposes.[9–14] The paradigm has the advantage of motivated study subjects which aids in the precision of determining the effects of the regional block. We therefore designed a randomized, triple blinded crossover-study in volunteers to evaluate the pharmacodynamic effects of dexamethasone as an additive to ropivacaine in a standardized peripheral nerve block.

Materials and Methods

Trial authorisation. We obtained approval of the study protocol from the institutional review board (ethics commission) at the Medical University of Vienna (ref. 1381/2018) and registered the study in the European Union Drug Regulating Authorities Clinical Trials (EudraCT, ref. 2018-001221-98) and the German Clinical Trial Register (DRKS, ref. 00014604).

Subjects. We recruited male volunteers aged 18 -55 years with body mass index (BMI) 18 -35 kg m^{-2} to receive ultrasound guided ulnar nerve blockade on three different days. The volunteers were recruited via the Department of Clinical Pharmacology of the Medical University of Vienna and paid according to the legal standards for payment of volunteers for clinical studies. Exclusion criteria were hypersensitivity or allergy to the study drugs or poor visibility of the ulnar nerve upon ultrasound at the projected puncture site (see below).

Ulnar nerve blockade. All ulnar nerve blocks were performed on the non-dominant side. The ulnar nerve was visualized using ultrasound (SonoSite X-Port™, Fujufilm SonoSite Inc., Bothell, WA, USA) below the level of the sulcus of the ulnar nerve and proximal to where the ulnar artery joins the nerve, between the flexor carpi ulnaris, humeroulnar head of the superficial flexor digitorum and flexor digitorum profundus muscles. At this site the ulnar nerve appears typically as a triangular structure (Figure 1). After insertion of a cannula (Venflon®) with a switch-valve into an antecubital vein (contralateral to the nerve block), the skin at and around the puncture site was prepared in a surgical sterile manner and the 15-7 MHz linear ultrasound probe was covered with a sterile ultrasound probe cover (SaferSonic Inc., Ybbs, Austria). Sterile ultrasound gel was used as contact medium between the ultrasound probe and the skin (SaferGel, SaferSonic Inc., Ybbs, Austria). For the nerve block we used 22G 50 mm Facette tip needles with an injection line (Polymedic™, te me na, Carrières sur Seine, France). An in-plane ultrasound needle technique was used to position the needle tip adajacent but extraepineurally to the nerve prior to administration of the study drugs (Figure 2). All nerve blocks were performed by one investigator (P.M.).

Study groups and dosing rationale. The *control* group received perineural ropivacaine 3 ml 0.75% wt/vol plus saline 1 ml (= ropivacaine 0.56% wt/vol) and iv saline 1 ml; the *perineural* group received perineural ropivacaine 3 ml 0.75% wt/vol (Naropin™, 7.5 mg mL^{-1}, AstraZeneca Ltd, Wedel, Germany) plus dexamethasone 4 mg (dexamethasone 8 mg / 2 ml, Organon Laboratories Ltd, Cambridge, UK) (= ropivacaine 0.56% wt/vol) and iv saline 1 ml; the *intravenous* group received perineural ropivacaine 3 ml 0.75% wt/vol plus saline 1 ml (= ropivacaine 0.56% wt/vol) and iv dexamethasone 4 mg (= 1 ml). The three nerve blocks were performed on three separate days with a minimum interval of 7 days between blocks, corresponding to approximately 5 times the half-life of dexamethasone and 30 times the half-life of ropivacaine.

Assessment of sensory block. Sensory blockade was assessed by using a visual analogue scale (VAS, 0-100 mm) in response to pinprick testing of the hypothenar area in comparison with the contralateral side, with 0 mm indicating no sharp sensation and 100 mm indicating the same sharp sensation as the unblocked limb. Five areas of sensory supply were defined: dorsal, ulnar and palmar aspects of the side of the hypothenar area, the little finger, and the ulnar side of the ring finger. Testing was performed before the block and then 2, 4, 6, 8, 10, 15, 20, 30 and 60 min after the block, and thereafter every 60 min. The onset of sensory block was defined as the time when the VAS score to pinprick testing was reduced to $\leq$ 10 mm in 4 of the 5 areas (see above). The duration of sensory block was defined as the time when the VAS to pinprick testing became $\geq$ 20 mm in one of the five areas.

Short bevel needles were used for pinprick testing. The tip of the needle was applied with a force sufficient to indent the skin without puncturing it: this produces a consistent unpleasant sharp sensation when applied to non-blocked areas. [15 16] All sensory tests were performed by two investigators (D.M. and M.R.B.).

Randomization. Randomization to study period sequence was done with a block size of 6 using an open access online randomization generator (www.randomization.com). Two sets (one main set, one backup set) of sealed envelopes with the randomization number containing information about the sequence of treatment allocation were prepared for each individual subject and kept throughout the study.

Blinding. The study drugs were prepared in a syringe by a study nurse. Immediately after the end of administration of study drugs, the subject was taken to a different room where a physician, unaware of the injected study drugs, performed and recorded the sensory tests to assess block success and duration. The subjects were unaware of the injected study drugs.

Study hypothesis. The null hypothesis was that there were no differences in the duration of sensory block between administration of perineural or intravenous dexamethasone in combination with perineural ropivacaine. The alternative hypothesis was that perineural or intravenous dexamethasone affected the duration of sensory block produced by perineural ropivacaine.

Primary and secondary outcomes. The primary outcome was the duration of sensory block and the secondary outcome was the time to onset of sensory block.

Post-study investigation. Within a week of the last study day, volunteers were examined for clinical signs of nerve damage (full recovery of the nerve block) and inflammation or infection of the puncture area.

Power and statistical analysis. A previous study with dexmedetomidine as the additive drug to ropivacaine showed that the duration of sensory blockade was increased from 8.7 to 21.4 h with the largest SD of 4 h.[11] To find a minimum clinically important difference in duration of sensory block of 4 h with at least 80% power, 24 volunteers are required (Bonferroni corrected $P = 0.017$ type 1 error rate for 3 comparisons) to keep the overall type 1 error rate at <5%.

Results are presented as mean (SD), median [interquartiles] and count as appropriate. Normality was assessed using histograms, normal probability plots and the D 'Agostino omnibus test. Data were analysed using mixed models with maximum likelihood estimation for repeated measures in a crossover design. This included tests for crossover sequence, treatment, period and treatment by period interactions. Nonparametric analyses including Friedman analysis were used as appropriate. Bonferroni correction (P <0.017) was applied for three comparisons to keep the overall type 1 error rate at < 5%. Significance was defined at $P < 0.05$ (two-sided). Analyses

was conducted using PASS 8.0, Number Cruncher Statistical Systems (NCSS) 12 and StatXact 9.

Results

Twenty-four volunteers were enrolled and 72 blocks were performed: the blocks were performed on the left arm in 19 volunteers and the right arm in 5. The volunteers had a median (range) age of 30 (22, 55) years and mean (SD) BMI of 23.7 (2.64) kg m^{-2}.

The duration of sensory block, as the primary outcome, was similar for the three interventions with no significant effect ($P = 0.61$) of perineural or intravenous dexamethasone 4 mg, as shown in Figure 3 and summarized in Table 1. Likewise, for the secondary outcome, time to onset of sensory block, there was no significant effect ($P = 0.16$) of dexamethasone 4 mg (Figure 4, Table 1).

Formal simultaneous crossover analyses for sequence ($P \geq 0.90$), period ($P \geq 0.29$) and period by treatment interactions ($P \geq 0.27$) using mixed models were not significant, suggesting no evidence of carry-over effects in the study.

At follow-up, all subjects had full recovery of sensation in the ulnar nerve distribution. There were no other sequalae of the study.

Discussion

This randomized crossover study in male volunteers found no clinically important or statistically significant effects of perineural or intravenous dexamethasone on sensory block with ropivacaine using a standardized peripheral nerve block model.

The pharmacodynamic effects of drugs co-administered with local anaesthetics are of particular interest. There have been no new local anaesthetic drugs introduced into clinical practice since ropivacaine and levobupivacaine more than 30 and 20 years ago, respectively. The recent re-launch of chloroprocaine, an aminoester local anaesthetic, which was developed 70 years ago, emphasises the lack of improved new agents for regional anaesthesia. Thus, adjuvants offer the only available possibility to improve the pharmacodynamic profile of nerve blocks. Alpha-2-receptor agonists,[11 17–19] opioids,[20] NMDA-receptor antagonists,[21] vasoconstrictors [22] or corticosteroids [1–7] have all been investigated for their potential to increase the duration of sensory blockade with local anaesthetics.

Dexamethasone has been extensively investigated as an additive drug to local anaesthetics for peripheral nerve blockade.[1–7] Table 2 summarizes the main findings of 7 meta-analyses of the use of dexamethasone in this context, and all authors highlight the low quality evidence provided by the source data. Heterogenous study designs using different types and concentrations of local anaesthetics with or without vasoconstrictors and a large variety of regional anaesthetic techniques and block sites are the main reasons for the problems when interpreting previous trials.

The disadvantage of most clinical studies in the field of regional anaesthesia, which are performed during the course of routine clinical practice, is the fundamental difficulty of accurately evaluating the pharmacodynamic characteristics of the block. First, there are logistical problems. Studies may rely on routine postoperative observations for the outcome data but the timing of these may not be sufficiently reliable because of the nature of busy clinical environments. Even if there are dedicated study personnel, the crucial endpoints may occur outside their working hours or, as often is the case nowadays, the patient may have been discharged from the hospital. For these reasons, patient reported outcomes are sometimes used but these may be unreliable if, for

example, sensation returns during the night, or the patient is otherwise distracted and is unable to record precise timings. The second cause of difficulty in evaluating the duration of blocks arises from the associated surgery: both sensory and motor function testing can be impeded by the surgical dressings, which very often will prevent access to the most invariable area of sensory innervation of the nerve in question. A third problem is the use of the time of onset of pain as a measure of sensory block duration. The inter-patient variability in pain perception is well known [23 24] but surgical pain can be an inappropriate outcome if the surgical site is not completely covered by the nerve block under investigation: this can be inconsistent between patients, even those having the same operation because of variability of sensory innervation.[25]

On the other hand, clinical studies in volunteers provide a highly standardized study environment with highly motivated study subjects, dedicated and trained study personnel and reproducible regional nerve block techniques. In particular the ulnar nerve serves as a well established model for such studies and shows a constant sensory distribution pattern with the lowest intra- and interindividual variability compared with other sensory- and motor nerves supplying the hand.[11 18 25] The other major advantage of our study was the opportunity to employ a crossover design that eliminated inter-individual variability in response to pinprick testing.

We administered 3 ml ropivacaine 0.56% wt/vol, a dose and concentration that is described as sufficient to provide a full sensory block at a peripheral nerve.[26] The effect on sensory block duration of perineural dexamethasone has been described as dose-independent between 4 and 10 mg,[1] and so we used 4 mg dexamethasone for both the *perineural* and *intravenous* groups. Four mg dexamethasone as additive to local anaesthetics is described as the lowest sufficient dose for peripheral nerve blockade in the literature.

We were unable to make a skin incision in our volunteers, so could not define the onset time of our blocks in relation to the time to achieve surgical anaesthesia. While complete loss of pinprick sensation is a better predictor of surgical anaesthesia [15 16] we defined onset time as the time to achieve VAS < 10 mm in response to pinprick because, in our experience, this is a more reproducible endpoint. Furthermore, we required this endpoint to be reached in only four out of 5 discrete sites of sensory

innervation of the ulnar nerve because of inter-patient variability in the sensory innervation of the hand.[25] We decided to define sensory block duration when the VAS in any one of the previously blocked areas reached > 20 mm on the VAS (and not back to 100 mm) firstly to avoid an extremely long study duration for our volunteers. However, this is perhaps more comparable to the clinically relevant post-surgical endpoint of the onset of postoperative pain.

This study had >99% power to find a difference of 4 h in the duration of sensory block that we decided to be the minimum important clinical difference when conducting our sample size calculations. The difference from the *a priori* power was because of the low root mean square error observed in this study (1.4 h) compared to the conservative SD of 4 h that was used in the original sample size calculations. We based our power calculation on data from the study by Keplinger et al.,[11] which used (the longer) duration until complete recovery from sensory block and it might be argued that a difference of less than 4 h using our endpoint might be clinically relevant. However, the present study still had 98% power to find a smaller difference of 2 h as significant.

Our study provides robust evidence that neither perineural nor intravenous dexamethasone prolongs sensory block duration of ropivacaine applied perineurally to the ulnar nerve. It is important to highlight that this study involved blockade of healthy nerves. It remains possible that dexamethasone as an additive to local anaesthetics may be useful in chronic pain therapy (e.g. neuropathic pain) through modulation of inflammatory changes or (similar to opioids) gene expression in affected nerves.[27] Nevertheless, any perineural administration of dexamethasone should consider a possible influence on nerval blood flow.[28] Further studies should investigate the use of dexamethasone as a perineural or additive drug in chronic pain therapy and the clinical impact on nerval blood flow.

In conclusion, we found no evidence of any beneficial effect of perineural or intravenous dexamethasone 4 mg in prolonging sensory block with ropivacaine following ulnar nerve block at the forearm in volunteers.

Authors contribution. Drs P. Marhofer, M. Columb, P.M. Hopkins and M. Zeitlinger contributed equally to analysing and interpreting the data and to drafting the manuscript. Dr D Marhofer was in charge of the administrative part (ethics committee, communication with the Austrian Agency for Health and Food Safety, trial registration). Dr Columb was involved in study design and analysis. Drs P. and D. Marhofer, M. Greher, M.R. Levi Bienzle and M. Zeitlinger contributed equally to the clinical management of the procedures for the volunteers.

Acknowledgements. We wish to thank Maria Weber (Study nurse at the Department of Clinical Pharmacology, Medical University of Vienna) and Valentin al Jalali (Department of Clinical Pharmacology, Medical University of Vienna) for their invaluable contribution during the entire study.

Declaration of interests. P.M. and P.M.H are board members of the *British Journal of Anaesthesia*, M.C. is and editorial board member of the *European Journal of Anaesthesiology* and research methods & statistical editor at the *British Journal of Anaesthesia*, all other authors declared no conflict of interest.

Role of the funding source. All financial support came from departmental sources.

List of references

1. Albrecht E, Kern C, Kirkham KR. A systematic review and meta-analysis of perineural dexamethasone for peripheral nerve blocks. Anaesthesia. 2015; **70**: 71-83.
2. Baeriswyl M, Kirkham KR, Jacot-Guillarmod A, Albrecht E. Efficacy of perineural vs systemic dexamethasone to prolong analgesia after peripheral nerve block: a systematic review and meta-analysis. Br J Anaesth. 2017; **119**: 183-91.
3. Choi S, Rodseth R, McCartney CJ. Effects of dexamethasone as a local anaesthetic adjuvant for brachial plexus block: a systematic review and meta-analysis of randomized trials. Br J Anaesth. 2014; **112**: 427-39.
4. Heesen M, Klimek M, Imberger G, Hoeks SE, Rossaint R, Straube S. Co-administration of dexamethasone with peripheral nerve block: intravenous vs perineural application: systematic review, meta-analysis, meta-regression and trial-sequential analysis. Br J Anaesth. 2018; **120**: 212-27.
5. Huynh TM, Marret E, Bonnet F. Combination of dexamethasone and local anaesthetic solution in peripheral nerve blocks: A meta-analysis of randomised controlled trials. Eur J Anaesthesiol. 2015; **32**: 751-58.
6. Pehora C, Pearson AM, Kaushal A, Crawford MW, Johnston B. Dexamethasone as an adjuvant to peripheral nerve block. Cochrane Database Syst Rev. 2017; **11**: CD011770.
7. Zhao WL, Ou XF, Liu J, Zhang WS. Perineural versus intravenous dexamethasone as an adjuvant in regional anesthesia: a systematic review and meta-analysis. J Pain Res. 2017; **10**: 1529-43.
8. Marhofer P, Columb M, Hopkins PM. Perineural dexamethasone: the dilemma of systematic reviews and meta-analyses. Br J Anaesth. 2018; **120**: 201-3.
9. Eichenberger U, Stöckli S, Marhofer P et al. Minimal local anesthetic volume for peripheral nerve block: a new ultrasound-guided, nerve dimension-based method. Reg Anesth Pain Med. 2009; **34**: 242-46.
10. Jæger P, Grevstad U, Koscielniak-Nielsen ZJ, Sauter AR, Sørensen JK, Dahl JB. Does dexamethasone have a perineural mechanism of action? A paired, blinded, randomized, controlled study in healthy volunteers. Br J Anaesth. 2016; **117**: 635-41.
11. Keplinger M, Marhofer P, Kettner SC, Marhofer D, Kimberger O, Zeitlinger M. A pharmacodynamic evaluation of dexmedetomidine as an additive drug to ropivacaine for peripheral nerve blockade: A randomised, triple-blind, controlled study in volunteers. Eur J Anaesthesiol. 2015; **32**: 790-96.
12. Madsen MH, Christiansen CB, Rothe C, Andreasen AM, Lundstrøm LH, Lange KHW. Local Anesthetic Injection Speed and Common Peroneal Nerve Block Duration: A Randomized Controlled Trial in Healthy Volunteers. Reg Anesth Pain Med. 2018; **43**: 467-73.
13. Marhofer D, Karmakar MK, Marhofer P, Kettner SC, Weber M, Zeitlinger M. Does circumferential spread of local anaesthetic improve the success of peripheral nerve block. Br J Anaesth. 2014; **113**: 177-85.
14. Marhofer P, Eichenberger U, Stöckli S et al. Ultrasonographic guided axillary plexus blocks with low volumes of local anaesthetics: a crossover volunteer study. Anaesthesia. 2010; **65**: 266-71.
15. Marhofer D, Marhofer P, Kettner SC et al. Magnetic resonance imaging analysis of the spread of local anesthetic solution after ultrasound-guided lateral thoracic paravertebral blockade: a volunteer study. Anesthesiology. 2013; **118**: 1106-12.

16. Curatolo M, Petersen-Felix S, Arendt-Nielsen L. Sensory assessment of regional analgesia in humans: a review of methods and applications. Anesthesiology. 2000; **93**: 1517-30.
17. Kelika P, Arun JM. Evaluation of clonidine as an adjuvant to brachial plexus block and its comparison with tramadol. J Anaesthesiol Clin Pharmacol. 2017; **33**: 197-202.
18. Marhofer D, Kettner SC, Marhofer P, Pils S, Weber M, Zeitlinger M. Dexmedetomidine as an adjuvant to ropivacaine prolongs peripheral nerve block: a volunteer study. Br J Anaesth. 2013; **110**: 438-42.
19. Patil KN, Singh ND. Clonidine as an adjuvant to ropivacaine-induced supraclavicular brachial plexus block for upper limb surgeries. J Anaesthesiol Clin Pharmacol. 2015; **31**: 365-69.
20. Heo BH, Lee HJ, Lee HG et al. Femoral nerve block for patient undergoing total knee arthroplasty: Prospective, randomized, double-blinded study evaluating analgesic effect of perineural fentanyl additive to local anesthetics. Medicine (Baltimore). 2016; **95**: e4771.
21. Lee IO, Kim WK, Kong MH et al. No enhancement of sensory and motor blockade by ketamine added to ropivacaine interscalene brachial plexus blockade. Acta Anaesthesiol Scand. 2002; **46**: 821-26.
22. Saied NN, Gupta RK, Saffour L, Helwani MA. Dexamethasone and Clonidine, but not Epinephrine, Prolong Duration of Ropivacaine Brachial Plexus Blocks, Cross-Sectional Analysis in Outpatient Surgery Setting. Pain Med. 2017; **18**: 2013-26.
23. Nielsen CS, Stubhaug A, Price DD, Vassend O, Czajkowski N, Harris JR. Individual differences in pain sensitivity: genetic and environmental contributions. Pain. 2008; **136**: 21-29.
24. Nielsen CS, Staud R, Price DD. Individual differences in pain sensitivity: measurement, causation, and consequences. J Pain. 2009; **10**: 231-37.
25. Keplinger M, Marhofer P, Moriggl B, Zeitlinger M, Muehleder-Matterey S, Marhofer D. Cutaneous innervation of the hand: clinical testing in volunteers shows high intra- and inter-individual variability. Br J Anaesth. 2018; **120**: 836-45.
26. Klein SM, Greengrass RA, Steele SM et al. A comparison of 0.5% bupivacaine, 0.5% ropivacaine, and 0.75% ropivacaine for interscalene brachial plexus block. Anesth Analg. 1998; **87**: 1316-19.
27. Ueda H. Molecular mechanisms of neuropathic pain-phenotypic switch and initiation mechanisms. Pharmacol Ther. 2006; **109**: 57-77.
28. Shishido H, Kikuchi S, Heckman H, Myers RR. Dexamethasone decreases blood flow in normal nerves and dorsal root ganglia. Spine (Phila Pa 1976). 2002; **27**: 581-86.

Table 1. Effects of dexamethasone 4 mg on sensory block duration and onset time.

Variable (N=24)	**Control**	**Perineural**	**Intravenous**	***P* value**
Duration (h)	6.87 [5.85 – 7.62]	7.37 [5.78 – 7.93]	7.37 [6.10 – 7.97]	0.61
Onset time (min)	6.0 [4.5 – 10.0]	8.0 [6.0 – 15.0]	8.0 [6.0 – 13.8]	0.16

Times are presented as median [IQR] with *P* values from mixed models analysis.

Table 2. Summarized results of meta-analyses investigating the effects of dexamethasone as an additive for peripheral nerve blockade on sensory block duration

	Included trials (no. of subjects)	**Dexamethasone dose (mg)**	**Local anaesthetics**	**Mean difference (95% CI) in sensory block duration (min)**	**Final conclusion**
Choi et al. 2014 [3]	9 (801)	4-10	Long acting	+ 576 (522 - 631)	Dexamethasone prolongs sensory duration, the effect of systemic administration must be evaluated
Albrecht et al. 2015 [1]	29 (1695)	4-10	Short, medium and long acting	+ 233 (172 - 295) with short and medium acting LA + 488 (419-557) with long acting LA	Interpret results with caution due to extreme heterogeneity of studies
Huynh et al. 2015 [5]	12 (1054)	4-10	Medium and long acting	+ 351 (288 - 413)	Significant prolongation of duration of peripheral nerve blockade
Zhao et al. 2017 [7]	10 (749)	4-10	LAs with or without epinephrine	+ 2 (-4 – 14) without epinephrine + 238 (160 – 316) with epinephrine	Increases the duration of sensory block only when epinephrine is also added

Baeriswyl et al. 2017 [2]	11 (914)	4-10	Short and long acting	+ 180 (84 – 270)	Sensory block increased by 21% with bupivacaine and 12% with ropivacaine, only a moderate quality of evidence
Pehora et al. 2017 [6]	35 (2702)	No information	Short, medium and long acting	+ 402 (332 – 471)	Low to moderate quality of evidence, IV dexamethasone increases block duration *vs* placebo, onging trials may change these results
Heesen et al. 2018 [4]	10 (783)	5-10	Short and long acting	+ 241 (87-394)	Low quality evidence

Legends to illustrations

Figure 1. High-resolution ultrasound image of the anatomical position of the ulnar nerve at the forearm between the superior flexor digitorum muscle (SFCM), profound flexor digitorum muscle (PFDM) and the flexor carpi ulnar muscle (FCUM). The ulnar nerve (indicated by the arrow) appears at this anatomical position as triangular structure and was the standardized site of nerve blockade.

Figure 2. High-resolution ultrasound image of the ulnar nerve blockade via an in-plane needle guidance technique. The vertical arrow indicates the shaft of the needle and the horizontal arrow indicates the tip of the needle. The administered local anaesthetic (with or without dexamethasone or saline) appears as hypoechoic area around the hyperechoic nerve.

Figure 3. Sensory block durations are shown for each volunteer showing the effects of perineural or intravenous dexmethasone 4 mg. Although the repeated measures are linked for the purposes of presentation, the order was randomized.

Figure 4. Sensory block onset times are shown for each volunteer showing the effects of perineural or intravenous dexmethasone 4 mg. Although the repeated measures are linked for the purposes of presentation, the order was randomized.

Figure 1

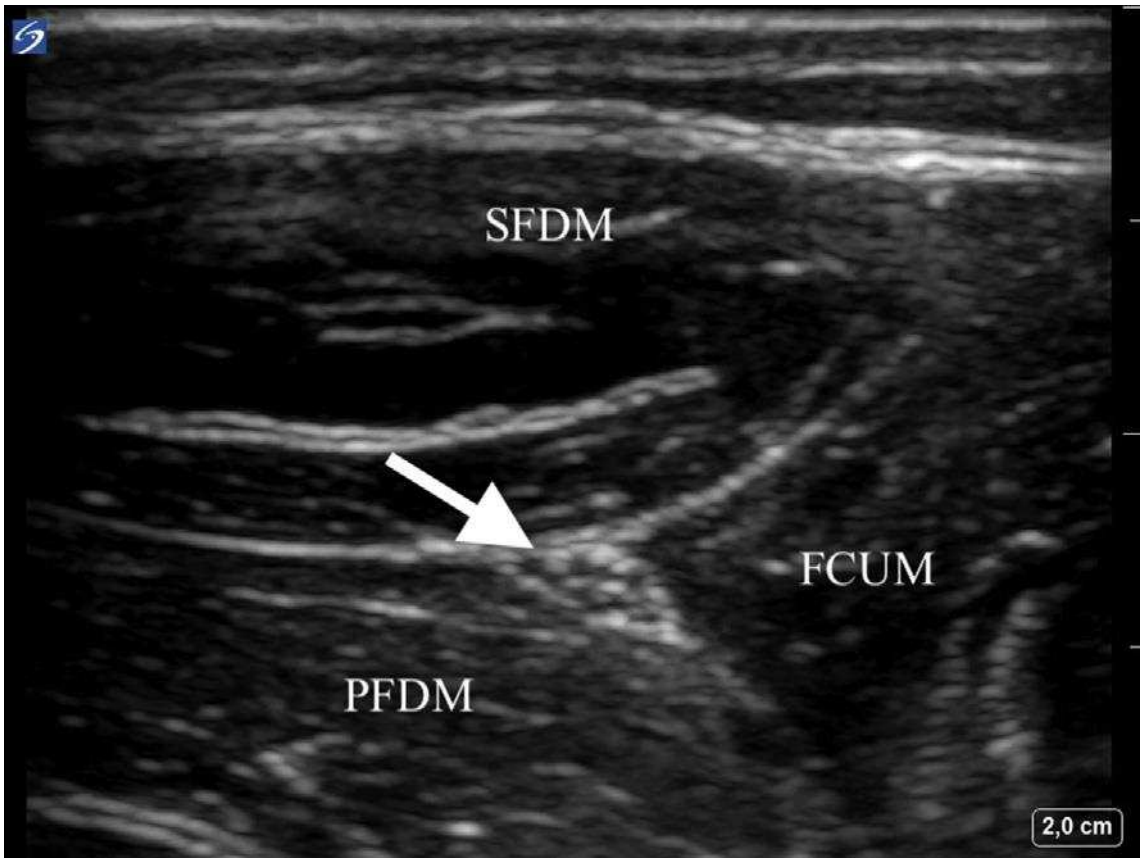


Figure 2

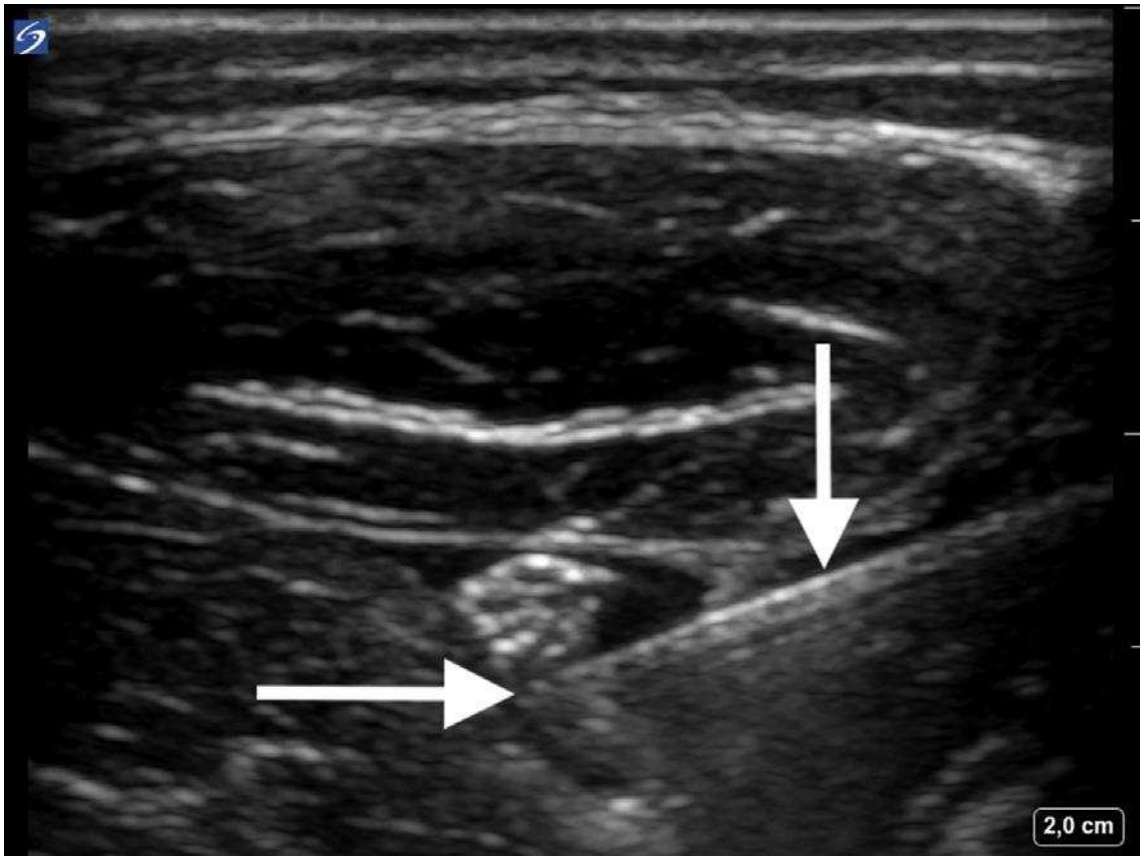
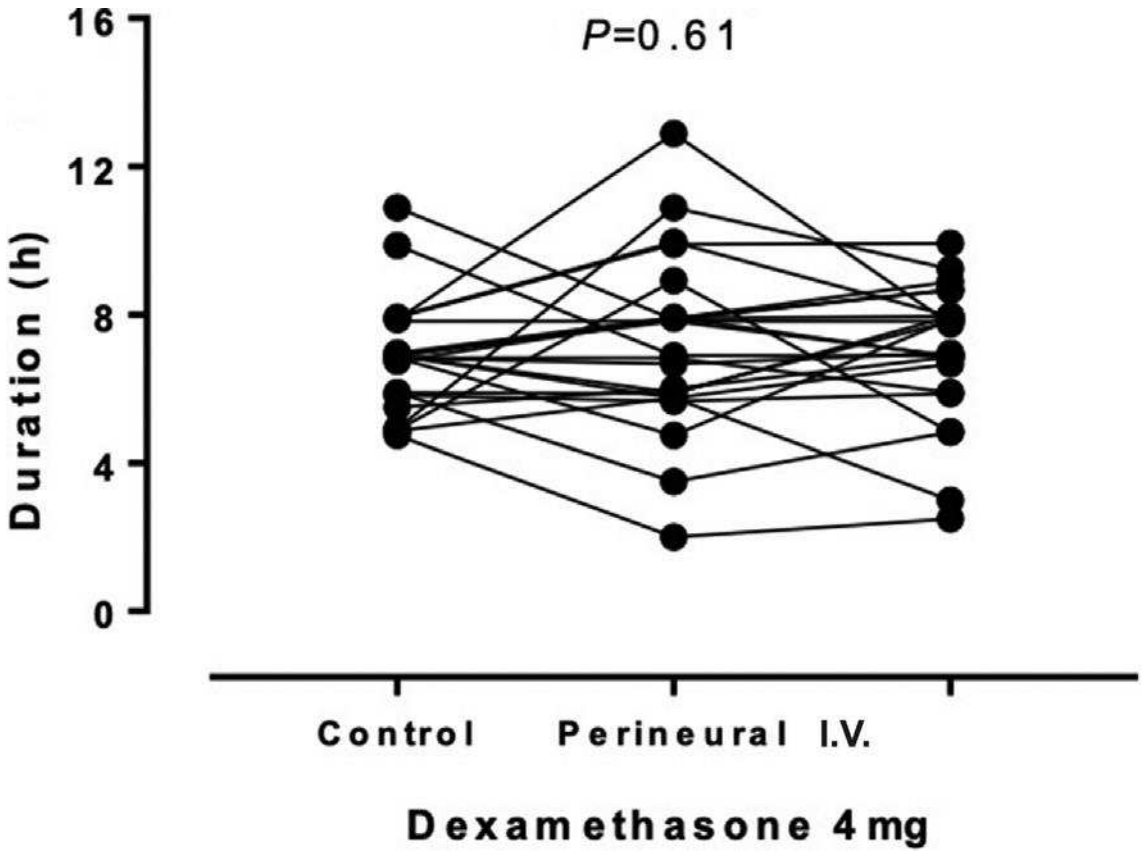


Figure 3


P=0.61
16
12
8
4
0
Duration (h)
Control
Perineural I.V.
Dexamethasone 4 mg

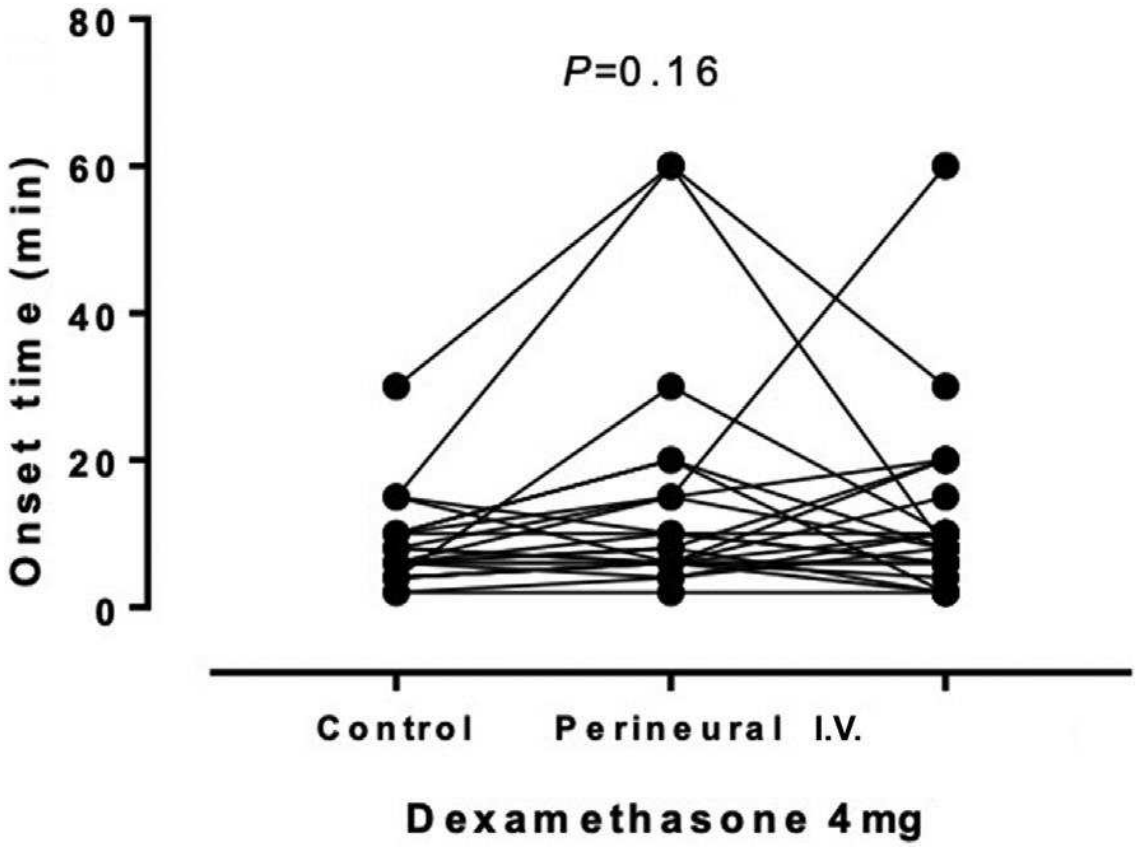

80
60
40
20
0
Onset time (min)
P=0.16
Control
Perineural I.V.
Dexamethasone 4mg

Figure 4