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Effects of vasoconstrictor use on digital nerve block: systematic review with meta-analysis.

Efeitos do uso de vasoconstritores no bloqueio de nervos digitais: revisão sistemática com metanálise.

Olimpio Barbosa da Silva Neto[1]; Cicero Felipe Paes de Araújo Costa[1]; Felipe Santiago Veloso[2]; Samir Buainain Kassar[1,2]; Demetrius Lucena Sampaio[1]

A B S T R A C T

Conventionally, the association of local anesthetics with vasoconstrictors is avoided at extremities due to the risk of ischemia. However, recent studies suggest that there is safety in the use of vasoconstrictors at extremities. Thus, we sought to evaluate the effectiveness and safety of vasoconstrictor use combined with local anesthetics in digital nerve block compared to the use of anesthetics without vasoconstrictors, through a systematic review with meta-analysis of randomized clinical trials. Until May 2019 we searched MEDLINE, LILACS, SciELO, ScienceDirect, Scopus, ClinicalTrials.gov, and gray literature databases, without date or language restrictions. The keywords were the following: digital block, vasoconstrictor, and ischemia. We included randomized clinical trials in which there was the use of local anesthetics with associated or not with vasoconstrictors in digital blocks. In the primary variables, the occurrence of ischemic complications and the duration of anesthesia were analysed; in the secondary variables, the need for anesthetic reapplication, bleeding control, and latency were observed. Ten studies were included in this review. The occurrence of ischemia was not observed, regardless of the use of vasoconstrictors or not. The use of vasoconstrictors at a concentration of 1:100,000 or less was associated with longer anesthesia duration (P<0.00001), lower need for anesthetic reapplication (P=0.02), lower need for bleeding control (P=0.00006), and lower latency (P<0.00001). We could conclude that the use of vasoconstrictors associated with local anesthetics in digital block proved to be a safe and effective technique.

Keywords: Ischemia. Anesthesia. Local. Fingers. Vasoconstrictor Agents.

INTRODUCTION

Minor surgeries and sutures on fingers are common procedures in the emergency department and surgical routine. Anesthetic blocks are essential for such procedures, as they guarantee pain relief. Anesthetic drugs, such as lidocaine, bupivacaine, and others[1], are used to perform blocks. When anesthetics are combined with a vasoconstrictor - epinephrine, most commonly - the duration of block is prolonged and systemic absorption and bleeding capacity are reduced. However, the combined use of local anesthetics with vasoconstrictors at extremities, such as fingers, penis, and nose, has been discouraged in medical practice for fear of causing ischemic events and even gangrene[2]. However, Denkler[3] had performed a literature review from 1880 to 2000, which has shown only 48 worldwide cases of digital gangrene associated with local anesthesia on fingers reported. Most of these studies were conducted before 1950, only 21 cases involving the use of epinephrine, 17 involving an unknown vasoconstrictor concentration, and none of them using lidocaine. On the other hand, researches show that the use of lidocaine with epinephrine in digital blocks seems to be safe, not causing digital gangrene[4-7].

Prospective study by Lalonde *et al*.[8], which has performed 3,110 elective lidocaine injections with epinephrine on fingers and hands, has not revealed any case of digital necrosis or need for reversal with phentolamine. Also Chowdhry *et al*.[9],

1 - Tiradentes University Center, Medicine Course, Maceió, AL, Brasil. 2 - State University of Health Sciences of Alagoas, Medicine Course, Maceió, AL, Brasil.

who have reviewed 1,111 cases involving the application of lidocaine associated with epinephrine in finger and hand procedures, have not found an increase in the risk of ischemia, but a decrease in the amount of anesthetic required, in the need for tourniquet use, and in the intraoperative bleeding. A Cochrane meta-analysis carried out in 2015, based on the use of only one local anesthetic, showed benefits in relation to anesthetic duration and intraoperative bleeding with the administration of lidocaine with epinephrine in comparison to full lidocaine in patients undergoing digital nerve block[10].

Thus, this systematic review with meta-analysis evaluated clinical trials in order to determine whether individuals undergoing digital block with any anesthetic combined with vasoconstrictor have been at higher risk of developing ischemic events and more or less favorable outcomes related to anesthesia duration, bleeding, latency, and need for new applications, when compared to individuals submitted to block without the addition of vasoconstrictor.

Search Strategy

The following databases were used by two independent researchers: MEDLINE, LILACS, SciELO, ScienceDirect, Scopus, and ClinicalTrials.gov. Additionally, the following gray literature databases were used: ClinicalEvidence.com and DissOnline. de. The search strategy included terms related to the intervention (use of anesthetics with vasoconstrictors for digital nerve block), primary variables (ischemic complications and anesthesia duration), and secondary variables (need for anesthetic reapplication, need for bleeding control, and anesthetic latency time). The search was done using MeSH terms and synonyms, without date or language restrictions, until May 2019. The complete search strategy is presented in the table below (Table 1).

Study Selection

The titles and abstracts of the papers identified in the search strategy were analysed by two independent proofreaders. According to the inclusion and exclusion criteria, duplicate studies were removed with the aid of Mendeley (version 1.01). In the next phase, the same proofreaders completely read the selected papers in order to independently verify the eligibility criteria. Papers with insufficient pieces of information in the abstract were also selected for full reading. In cases of disagreement, a third evaluator was consulted.

Eligibility Criteria

Only randomized clinical trials which met the following criteria were included:

Table 1. *Search strategy.*

Criterion 1	(randomized-controlled-trial/ or randomization/ or controlled-study/ or multicenter-study/ or phase-3-clinical-trial/ or phase-4- clinical-trial/ or double-blind-procedure/ or single-blind-procedure/ or (random or multicenter or factorial or placebo or volunteer) or (blind or mask) not (animals not (humans and animals)).
Criterion 2	(Epinephrine/ and Lidocaine) or ((adrenalin or epinephrine) and lidocaine) and ((Nerve Block/ or ((nerve block or injury) or (digit or finger)) and (bupivacaine and epinephrine) or (bupivacaine and vasoconstrictor) or (vasoconstrictor and anaesthesic local).
Criterion 3	1 and 2

patients from two months of age, regardless of gender or race, who required digital blocks with or without vasoconstrictors for procedure performance. Exclusion criteria were the following: 1) use of other substances not characterized as anesthetics or vasoconstrictors; 2) duplicate publications; 3) studies with conflict of interests; 4) studies with individuals presenting comorbidities, such as peripheral vascular disease, allergy to local anesthetics, pregnant women, history of cardiovascular or hepatic disease, and previous hand pathology (e.g. Raynaud's phenomenon).

Data Extraction

Data were independently extracted by the proofreaders, using a standardized table which comprised the sample characterization and the description of the intervention (type of anesthetic, dose, dilution, and number of blocks). The primary outcome was whether or not there would be a difference in the incidence of ischemic events among the studied groups. The secondary outcomes were the comparison of the mean anesthesia duration (in hours), mean differences among the need for anesthetic reapplication (in units), need for bleeding control (in units), and latency values (in minutes). All the necessary pieces of information were extracted from the published papers, protocols, and comments related to each study. Any disagreements were resolved by consensus among the researchers.

Included Studies

We identified 1,167 potentially relevant studies from the searched databases, according to the formulated search algorithm. Of these, 138 duplicates were excluded and, of the remaining 1,029, 55 papers were chosen based on their titles and compatibility with the inclusion criteria. These papers had their abstracts read, and ten of them were selected for full-text evaluation for eligibility and later included in the qualitative analysis (Table 2)[6,7,11-18].

Table 2. *Characteristics of the included studies*

Study	Year	Participants	Number of blocks	M/F	Anesthetic(s)	Vasoconstrictor	Dilution	Dose
Sönmez *et al*.[6]	2008	20	20	16/4	Lidocaine	Epinephrine	1:80,000	3ml
Alhelail *et al*.[7]	2009	12	24	8/4	Lidocaine/ Bupivacaine	Epinephrine	1:100,000	1ml
Altinyazar *et al*.[11]	2010	44	44	23/21	Lidocaine	Epinephrine	1:100,000	-
Andrades and Olguin[12]	2003	43	50	33/10	Lidocaine	Epinephrine	1:100,000	1.5ml
Calder *et al*.[13]	2013	42	42	19/23	Bupivacaine	Epinephrine	1:200,000	2ml
Córdoba-Fernández *et al*.[14]	2019	112	112	28/28	Lidocaine/ Bupivacaine	Epinephrine	1:100,000 1:200,000	2ml
Sonohata *et al*.[15]	2012	9	18	7/2	Lidocaine	Epinephrine	1:100,000	3ml
Thomson and Lalonde[16]	2006	30	90	-	Lidocaine/ Bupivacaine	Epinephrine	1:100,000	1.8ml
Todd *et al*.[17]	1992	20	20	-	Lidocaine	Epinephrine	1:100,000	1ml
Wilhelmi *et al*.[18]	2001	60	60	-	Lidocaine	Epinephrine	1:200,000	3ml

M/F: proportion of male and female individuals.

However, for the meta-analysis, seven of the ten papers were used. The flow diagram below illustrates the entire research process, selection, and inclusion of studies (Figure 1).

Meta-Analysis

Secondary variables analysed by meta-analysis in forest plot were: comparison of mean anesthesia duration (in hours; continuous variable), mean differences between the need for anesthetic reapplication (in units; dichotomous variable), need for bleeding control (in units, dichotomous variable), and latency values (in minutes; continuous variable).

RESULTS

Data Analysis and Meta-Analyses

Anesthesia duration

Andrades and Olguin[12] have designed a two-group randomized clinical trial in which 2% full lidocaine has been administered in one group and 2% lidocaine with epinephrine, in the other. This second group has benefited from longer anesthesia duration, which has been of 4.6 hours of anesthesia on average ($p<0.05$).

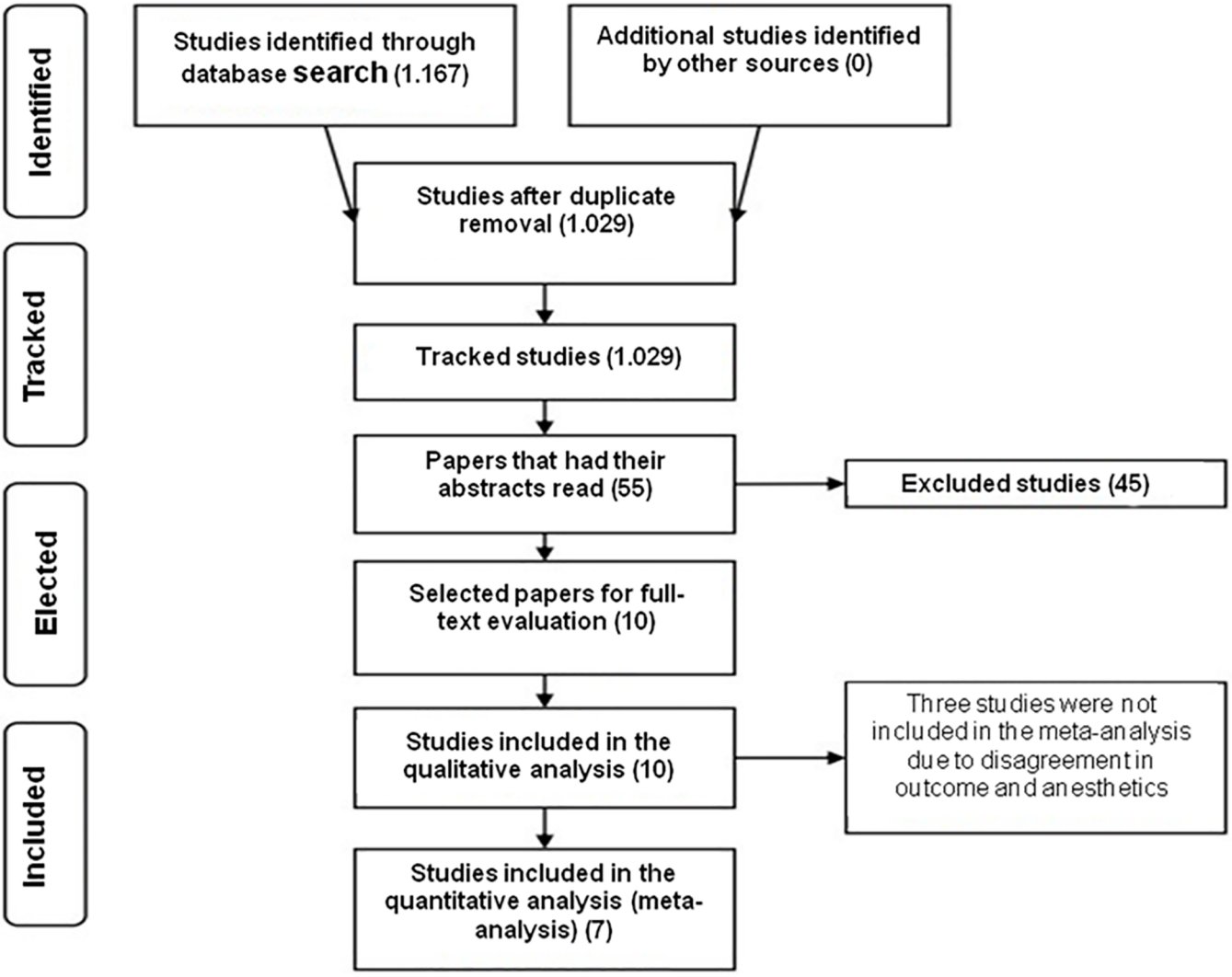

Figure 1. *Flow diagram of the paper selection process for meta-analyses.*

Sönmez *et al*.[6] have observed in their randomized clinical trial that, between the two analysed groups, the one which has received 2% lidocaine with 1:80,000 epinephrine has presented longer anesthesia duration, with an average of eight hours (p<0.001).

Sonohata *et al*.[15] have elaborated a clinical trial with volunteers in which 1% full lidocaine and 1% lidocaine with epinephrine have been administered. The second group has had, on average, 280.7 minutes of anesthesia, what has ensured longer time compared to the first group (p<0.01).

Thomson and Lalonde[16] have used 30 volunteers for the performance of a double-blind study in which 2% lidocaine, 2% lidocaine with 1:100,000 epinephrine, and 0.5% bupivacaine have been used. The longest anesthetic duration has been obtained with the use of bupivacaine. However, this meta-analysis has compared only lidocaine solutions, of which the association with epinephrine has been beneficial for the outcome, with average of 10.4 hours of anesthesia (p=0.01).

Todd *et al*.[17], through their clinical trial, have found that the group that has undergone 1% lidocaine injection with epinephrine has had a longer anesthetic duration of 8.1 hours (p<0.01).

Individuals who have received anesthetic with vasoconstrictors have had longer duration (in hours) of anesthesia. The meta-analysis evaluating this outcome is shown in figure 2 (95%CI, P<0.00001, I^2=89%, P<0.00001).

Need for anesthetic reapplication

Andrades and Olguin[12] have presented a randomized clinical trial comparing lidocaine with epinephrine with full lidocaine in relation to the need for anesthetic reapplication in digital nerve block. The group using lidocaine with epinephrine has had less need for anesthetic reapplication when compared to the group using lidocaine alone (RR 0.17; 95%CI: 0.02-1.55).

Wilhelmi *et al*.[18] have observed in their clinical trial study that the application of lidocaine with epinephrine compared to full lidocaine decreases the need for anesthetic reapplication (RR 0.13; 95%CI: 0.01-1.14). The meta-analysis of the studies by Andrades and Olguin[12] and Wilhelmi *et al*.[18] is shown in figure 3 (95%CI, P=0.02, I^2=0%, P=0.90).

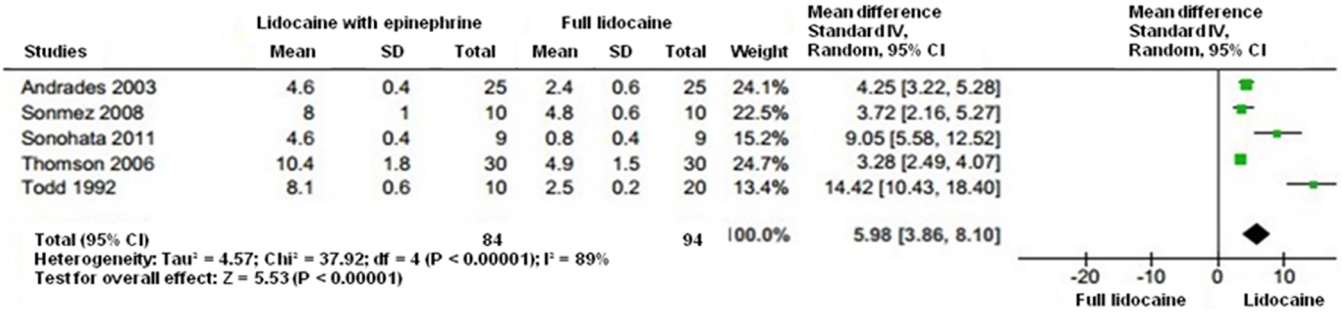

Figure 2. *Duration (in hours) of anesthesia with and without vasoconstrictor. SD: standard deviation; CI: confidence interval.*

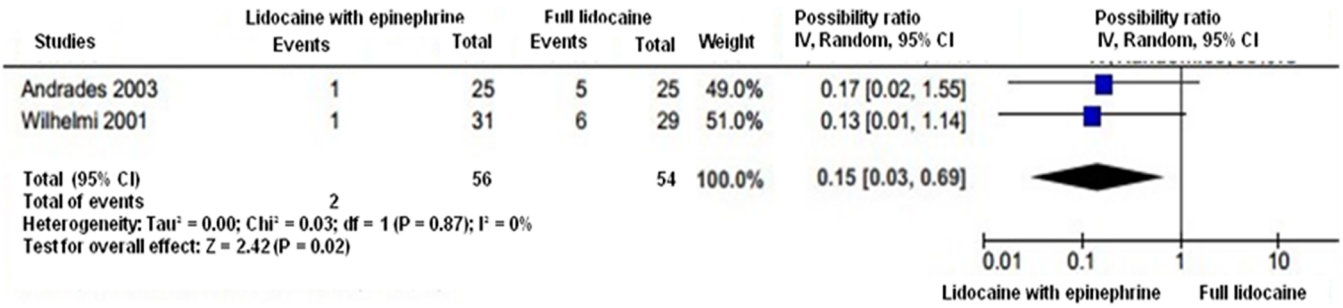

Figure 3. *Need for anesthetic reapplication. SD: standard deviation; CI: confidence interval.*

Need for bleeding control

In their clinical trial, Andrades and Olguin[12] have compared the application of lidocaine with epinephrine and full lidocaine in relation to the need for bleeding control, concluding that the addition of epinephrine to the digital block has significantly reduced the need for bleeding control (RR 0.07; 95%CI: 0.00-1.40).

Wilhelmi *et al*.[18] have demonstrated in their study the superiority of the use of lidocaine with epinephrine when compared to full lidocaine in relation to the need for bleeding control (RR 0.18; 95%CI: 0.16-0.46). Figure 4 represents the meta-analysis of the studies mentioned above (95%CI, P=0.00006, I^2=0%, P=0.57).

Latency

Córdoba-Fernández *et al*.[14] studied a total of 56 patients, divided into two groups of 28 patients each, in order to evaluate the anesthetic latency of lidocaine with vasoconstrictor compared to full lidocaine. The mean latency (in minutes) of the anesthetic with vasoconstrictor has been of 1.56 minutes, while the latency of full lidocaine has been of 2.25 minutes (RR -1.24; 95%CI: -1.82 - -0.67).

Sonohata *et al*.[15] have analysed the anesthetic latency of lidocaine with vasoconstrictor compared to full lidocaine and concluded that the addition of epinephrine has significantly decreased the anesthetic latency time (RR -1.36; 95%CI: -2.41 - -0.31). Figure 5 represents the meta-analysis of the studies mentioned above (95%CI, P≤0.00001, I^2=0%, P=0.85).

DISCUSSION

This review showed similar results to previous ones. Individuals submitted to anesthesia with vasoconstrictor obtained better and significant responses regarding anesthesia duration, need for anesthetic reapplication, bleeding control, and latency.

A study by Calder *et al*.[13] has consisted of two control groups: one with full bupivacaine and the other with bupivacaine associated with epinephrine. The conclusions inferred from this study using bupivacaine have been similar to the ones from other studies using lidocaine. The times of initial pain return (P=0.005), complete pain return (P=0.024), tactile sensation (P=0.004), and pressure sensation (P=0.004) have significantly been shorter in the group submitted to anesthesia with vasoconstrictor.

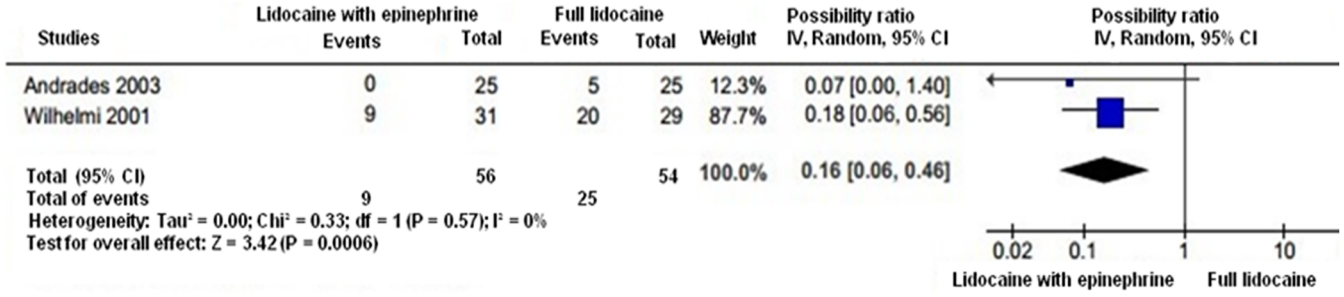

Figure 4. *Need for bleeding control. SD: standard deviation; CI: confidence interval.*

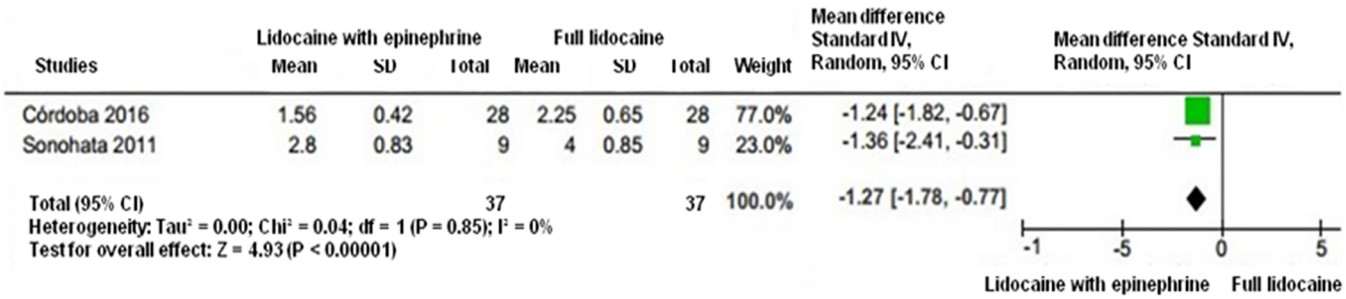

Figure 5. *Anesthetic latency with and without vasoconstrictor (in minutes). SD: standard deviation; CI: confidence interval.*

The times to return of pain sensation have begun after 15 hours (SD 3.25 hours) in the full bupivacaine group and after 16.4 hours (SD 2.40 hours) in the group using bupivacaine associated with epinephrine. Pain sensation has completely returned after 18.6 hours (SD 4.06 hours) in the full bupivacaine group, whereas, in the group using bupivacaine associated with epinephrine, it has returned after 19.6 hours (SD 3.52 hours). Tactile sensation has begun to return after 15.6 hours (SD 4.64 hours) for bupivacaine, while bupivacaine with epinephrine has shown tactile return after 17.3 hours (SD 3.50 hours). Pressure sensation has begun to return after 13.9 hours (SD 3.67 hours) in patients receiving bupivacaine alone *versus* 15.5 hours (SD 2.48) in patients receiving bupivacaine associated with epinephrine.

Other outcomes that could not be included in the quantitative analysis will be described in this discussion, such as oxygen saturation (SO_2), evaluated in the studies by Córdoba-Fernández *et al*.[14], Sonohata *et al*.[15], and Sönmez *et al*.[6]. In the study by Cordoba-Fernández *et al*.[14], 112 individuals have been divided into four groups (full lidocaine, lidocaine with epinephrine, full bupivacaine, and bupivacaine with epinephrine) and then analysed. SO_2 has significantly been lower in the groups with epinephrine during minutes 5 (P=0.041) and 10 (P=0.043). In its turn, the study by Sonohata *et al*.[15] has evaluated nine volunteers submitted to lidocaine with and without epinephrine at different times (P<0.01). SO_2 has significantly been lower at minute 20, during administration of full lidocaine. While Sönmez *et al*.[6] have evaluated 20 patients divided into two groups (full lidocaine and lidocaine with epinephrine). Their results have shown that SO_2 has significantly been higher after the administration of full lidocaine, at the time in which SO_2 of the group using lidocaine with epinephrine has not had significant difference before and after injection (P=0.017). Therefore, in these studies, there has been no significant difference in the administration of anesthetics with and without vasoconstrictor regarding SO_2.

Serum pH has been evaluated by Sönmez *et al*.[6] who demonstrated that, in the group using lidocaine with epinephrine there has been a slight increase in pH, from 7.395 to 7.403 (P=0.032), ten minutes after anesthetic administration. This increase has been corroborated by the slight decrease in pCO_2 and the slight increase in HCO_3, but not statistically significant.

The study presented by Altinyazar *et al*.[11] (44 patients) has shown that individuals submitted to lidocaine and epinephrine block (2.2±0.4ml) have had a mean anesthetic volume lower than the one presented by indivulduals submitted to full lidocaine (3.1±0.6ml). The injection of an excessive volume of local anesthetic may cause irreversible damages to digital vessels. The use of local anesthetics containing epinephrine may decrease the risk of damages related to the injected volume.

No ischemic event has been reported in the papers included in this review. In addition, other studies, such as the ones by Lalonde *et al*.[8], Chowdhry *et al*.[9], and Sardenberg *et al*.[19], have not shown any case of ischemia either. They have performed 488 wrist, hand, and finger surgeries using local anesthesia with lidocaine associated with epinephrine.

CONCLUSION

The use of local anesthetics associated with vasoconstrictors (at a concentration of 1:100,000 or less) in digital block proved to be a safe local anesthetic technique without ischemic complications, besides providing better visualization of the surgical field, allowing surgical procedures to be performed without the need for bleeding control measures, and benefiting patients with longer anesthesia duration.

R E S U M O

Convencionalmente, a associação de anestésicos locais com vasoconstritores é evitada em extremidades pelo risco de isquemia. Entretanto, estudos recentes sugerem haver segurança no uso de vasoconstritor em extremidades. Procuramos, assim, avaliar a efetividade e segurança do uso de vasoconstritores combinados com anestésicos locais no bloqueio de nervos digitais em comparação ao uso de anestésicos plenos, através de uma revisão sistemática com metanálise de ensaios clínicos randomizados. Pesquisamos, até maio de 2019, nas bases de dados MEDLINE, LILACS, SciELO, ScienceDirect, Scopus, ClinicalTrials.gov e literatura cinzenta, sem restrições de data ou idioma, os descritores: bloqueio digital, vasoconstritor e isquemia. Foram incluídos ensaios clínicos randomizados nos quais houve a utilização de anestésicos locais associados ou não a vasoconstritores em bloqueios digitais. Nas variáveis primárias foram analisadas a ocorrência de complicações isquêmicas e a duração da anestesia, e nas variáveis secundárias foram observadas necessidade de reaplicação anestésica, de controle de sangramento e latência. Dez estudos foram incluídos nesta revisão. Não foi observada a ocorrência de isquemia, independente do uso ou não de vasoconstritores. O uso de vasoconstritores na concentração de 1:100.000 ou menor esteve associado a maior duração da anestesia (P<0,00001), menor necessidade de reaplicação anestésica (P=0,02), menor necessidade de controle de sangramento (P=0,00006) e menor latência (P<0,00001). Pudemos concluir que uso de vasoconstritores associados a anestésicos locais no bloqueio digital mostrou-se uma técnica segura e efetiva.

Descritores: *Isquemia. Anestesia Local. Dedos. Vasoconstritores.*

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Mailing address:
Olimpio Barbosa da Silva Neto
E-mail: olimpio.barbosa95@gmail.com