Non-alkalinized and alkalinized 2-chloroprocaine *vs* lidocaine for intravenous regional anesthesia during outpatient hand surgery

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Purpose: Chloroprocaine should be an ideal agent for intravenous regional anesthesia (IVRA) because of its rapid onset and ester hydrolysis. Raising the pH of local anesthetics may increase the speed of onset and the intensity of nerve blocks. We compared plain and alkalinized 2-chloroprocaine 0.5% with lidocaine for IVRA.

Methods: In two separate double-blind studies, 78 patients scheduled for daycare hand surgery were randomized to receive 40 mL plain 2-chloroprocaine 0.5%, alkalinized 2-chloroprocaine 0.5% or lidocaine 0.5% for IVRA. Time to sensory and motor block, need for supplemental analgesia, and side effects were compared.

Results: There was no difference in time to sensory or motor block in either group. Patients who received plain chloroprocaine required more supplemental opioid and had a higher incidence of metallic taste and of hives than patients who received lidocaine ($P < 0.05$). Comparing alkalinized chloroprocaine with lidocaine, there was no difference found with respect to opioid supplementation, CNS side effects, or incidence of hives.

Conclusion: In conclusion, alkalinized chloroprocaine was found to be an effective agent for IVRA but no benefit over lidocaine was detected. Plain chloroprocaine for IVRA produced more minor side effects than lidocaine.

Objectif : La chloroprocaine est un agent idéal pour l'anesthésie régionale intraveineuse (ARIV) étant donné sa rapidité d'action et l'hydrolyse des esters. En élevant le pH des anesthésiques locaux, on peut accélérer le début de l'action et augmenter l'intensité des blocages nerveux. Nous avons comparé la 2-chloroprocaine simple 0,5 % et alcalinisée avec la lidocaïne pour une ARIV.

Méthode : Il y a eu deux études séparées, à double insu, auprès de 78 patients dont l'opération d'une main avait été prévue en chirurgie d'un jour et qui ont été répartis au hasard afin de recevoir 40 mL de 2-chloroprocaine simple 0,5 %, ou alcalinisée, ou de la lidocaïne 0,5 % pour une ARIV. Le temps nécessaire pour atteindre le blocage sensitif et moteur, les besoins d'analgesie supplémentaire et les effets secondaires ont été comparés.

Résultats : Il n'y a pas eu de différence intergroupe quant au temps nécessaire au blocage sensitif et moteur. Les patients qui ont reçu la chloroprocaine simple ont demandé plus d'opioïdes supplémentaires et ont présenté une plus forte incidence de goût métallique et d'urticaire que les patients qui ont reçu la lidocaïne ($P < 0,05$). Par contre, il n'y a pas eu de différence intergroupe entre les patients qui ont reçu la chloroprocaine alcalinisée et ceux qui ont reçu la lidocaïne.

Conclusion : La chloroprocaine alcalinisée a été jugée efficace comme agent d'ARIV, mais n'a pas présenté d'avantage par rapport à la lidocaïne. La chloroprocaine simple a produit plus d'effets secondaires mineurs que la lidocaïne.

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AUGUST BIER'S intravenous regional anesthesia (IVRA) remains a safe and reliable technique for upper extremity anesthesia.¹ It is particularly advantageous in ambulatory surgery since little, if any, adjunctive parenteral supplementation is required, and the rapid recession of anesthesia following tourniquet deflation allows early discharge. In North America, lidocaine 0.5% is the standard agent for IVRA.¹

With modern surgical techniques and shorter procedure duration, lidocaine has become less ideal. Potential disadvantages of lidocaine for IVRA include the risk of systemic toxicity after tourniquet deflation. Dunbar and Mazze reported a 2.1% incidence of mild central nervous system (CNS) toxicity with lidocaine for IVRA,² but more serious complications including seizures, cardiac arrest and death have also been described.¹

In contrast, 2-chloroprocaine may be an ideal agent for IVRA. Chloroprocaine has a rapid onset and is ester-hydrolyzed resulting in low plasma concentration which, theoretically, should hasten onset, intensify block, and minimize toxicity. The use of chloroprocaine for IVRA diminished in the 1960s due to a high incidence of venous thrombophlebitis.³ After changing the preservative from methylparaben, there have been no signs of thrombophlebitis in repeat investigations using 2-chloroprocaine for IVRA.⁴

Raising the pH of local anesthetics has been advocated to speed the onset and increase the intensity of nerve block. However, results obtained from alkalization of lidocaine and prilocaine for IVRA have been contradictory.⁵⁻⁷

The clinical efficacy of 2-chloroprocaine for IVRA and the effects of pH adjustment were studied in the outpatient setting in two parts. The first study compared plain 2-chloroprocaine with lidocaine for IVRA in endoscopic carpal tunnel release and the second investigation compared alkalized 2-chloroprocaine with lidocaine in outpatient hand surgery.

Methods

Each study was conducted as a single-centre, randomized, prospective double-blind trial. Institutional ethics approval was obtained along with written informed consent from each patient enrolled. Exclusion criteria were: patient refusal, age < 18 yr, allergy to local anesthetic, local infection, and heart block.

Plain chloroprocaine vs lidocaine

Thirty-eight ASA 1 and 2 daycare patients scheduled for elective endoscopic carpal tunnel release were enrolled. Patients were randomized to two groups. Group 1 received 40 mL lidocaine 0.5% and Group 2

FIGURE Sites used for sensory testing. 1. Forearm (musculotaneous nerve); 2. Thenar eminence (median nerve); 3. Index finger (median nerve); 4. Little finger (ulnar nerve); 5. Hypothenar eminence (ulnar nerve); 6. First webspace (radial nerve).

received 40 mL 2-chloroprocaine 0.5%. No premedication was given. Patients had an intravenous (*iv*) infusion established in the non-operative arm. In the operating room, patients were monitored with ECG, pulse oximeter, and automatic blood pressure cuff. A 22 g *iv* cannula was inserted distally in the dorsum of the operative hand; the arm exsanguinated with an Esmarch bandage; and a double cuff arm tourniquet inflated to 250 mm Hg. Solutions were prepared and drawn into coded syringes by an anesthesiologist not performing the block. Forty millilitres local anesthetic were injected over 60 sec, and the end of injection was considered to be time 0. Patients received a standard volume of local anesthetic rather than a $\text{mg}\cdot\text{kg}^{-1}$ dose. In an effort to minimize inter-observer variability, all observations were made by a single blinded investigator.

Sensory block was tested every two minutes using pinprick at standard sites in the distribution of ulnar, median, radial and musculocutaneous nerves as per Armstrong *et al.* (Figure).⁸ The site was considered blocked when pinprick was felt as blunt. VAS scores on a linear scale from zero to ten were made at two-minute intervals, starting before the actual incision, to standardize the results and to evaluate pain at the time of injection. Fentanyl was given as supplemental analgesia to patients who appeared to be uncomfortable during the procedure and responded positively when asked if the required analgesia, and the total dose

recorded. Motor block was graded as present or absent for flexor pollicis longus, the first and second dorsal interossei and flexor digitorum profundus. The tourniquet was deflated in a single step, and at that time, the patient was questioned regarding: dizziness, lightheadedness, tinnitus, perioral numbness, metallic taste, nausea, and muscle twitching. The operative arm was evaluated in the recovery room for hives.

Alkalinized chloroprocaine vs lidocaine

Forty ASA 1 and 2 surgical daycare patients scheduled for elective hand surgery were enrolled. Patients were randomized to receive either 40 mL lidocaine 0.5% or 40 mL 2-chloroprocaine 0.5% pH-adjusted from 4.0 to 7.6. Alkalinization was achieved by adding 4 mL sodium bicarbonate 8.4% to 30 mL 2-chloroprocaine 2% and subsequent dilution with normal saline to 0.5%. The volume of bicarbonate was determined from a bench study and is similar to that previously reported.⁵ Sensory and motor testing were as described above. Pain was recorded at the time of incision as present or absent. Alfentanil was used to supplement analgesia if required and the total dose recorded. Evaluation of side effects was as described above.

STATISTICAL METHODS

Plain chloroprocaine vs lidocaine

All the continuous data were skewed or bimodal, and therefore treated as non-parametric. Pain scores and total dose of fentanyl were collapsed to present versus absent categories due to the high proportion of zero scores. Fentanyl dosing, VAS pain, patient sex, incidence of side effects, sensory and motor block were summarized as counts (%), and analyzed for between group differences using chi-square or Fisher's exact test. Age, height, weight, tourniquet time, time to full motor block, and time to block each muscle group were summarized as medians and ranges, and between group comparisons made with the Mann-Whitney U test. Bonferroni's correction was used for multiple comparisons. An alpha level of 0.05 was chosen as the cutoff for statistical significance.

Alkalinized chloroprocaine vs lidocaine

Data were analyzed using unpaired t tests for age and height. Mann-Whitney U-test was used to compare weight, tourniquet time, and number of sites blocked at 5 and 10 min. Sensory and motor block at 5- and 10-min intervals were compared; as these would be realistic surgical start times after preparing and draping the skin. Chi-square or Fisher's Exact test was used to compare patient sex, alfentanil dosing, incisional pain, side effects, and motor block. Bonferroni's correction was applied for multiple comparisons. A P value of less than

0.05 was considered statistically significant.

Results

Plain chloroprocaine vs lidocaine

There were no differences between the two treatment groups in any of the measured demographic data (Table I). Surgical times for this procedure were brief, as reflected by short tourniquet times. In several cases, the cuff was deflated before 20 min, but tourniquet time was never < 15 min. There were no differences between groups in: time to sensory block; number of sites blocked at any given time; time to motor block; and pain.

In the chloroprocaine group, a higher proportion of patients required fentanyl (66.7%) than in the lidocaine group (20%) ($P = 0.003$). None of the lidocaine group experienced metallic taste after cuff deflation, while 22% of patients in the chloroprocaine group did ($P = 0.014$) (Table II). Hives were seen on the skin of the operative arm in 27.8% of the chloroprocaine group ($P = 0.017$) but there were no systemic manifestations of allergic reaction in any patient. There were no differences between the groups in the incidence of other side effects.

Alkalinized chloroprocaine vs lidocaine

There were no differences between the two treatment groups in any of the measured demographic variables (Table III). Many procedures were short but the aver-

TABLE I Demographics, tourniquet time and narcotic supplementation for plain chloroprocaine vs lidocaine.

	2-CP	Lidocaine
Sex F/M	12/6	14/6
Age (yr)	48 (35-80)	52 (32-80)
Ht (cm)	162 (153-177)	161.5 (142-180)
Wt (kg)	78 (54-126)	69 (51-114)
Tourniquet time (min)	18.5 (15-28)	20.5 (15-32)
Fentanyl supplementation	66.7%	20%*

Data are presented as median (range); * $P < 0.05$

TABLE II 2 Side effects for plain chloroprocaine vs lidocaine.

	2-CP	Lidocaine
Dizziness	10 (55.6%)	6 (30%)
Lightheadedness	8 (44.4%)	6 (30%)
Tinnitus	2 (11%)	3 (15%)
Perioral numbness	2 (11%)	0
Metallic taste	4 (22%)*	0
Nausea	3 (16.7%)	2 (10%)
Twitching	0	0
Hives	5 (27.8%)*	0

Data are presented as n (%), * $P < 0.05$

TABLE III Demographics and tourniquet time for alkalinized chloroprocaine *vs* lidocaine.

	2-CP(alk)	Lidocaine
Sex F/M	8/12	13/7
Age(yr)	55.9 ± 15	51 ± 16
Ht (cm)	167.8 ± 10.8	165.6 ± 11.5
Wt (kg)	68.5 (56-114)	68.6 (46-116)
Time (min)	32 (19-57)	26.5 (16-60)

Data presented as mean ± SD and median (range)

TABLE IV Side effects for alkalinized chloroprocaine *vs* lidocaine.

	Alk-2CP (N = 20)	Lidocaine (N = 20)
Dizziness	0	2 (10%)
Lightheadedness	1 (5%)	1 (5%)
Tinnitus	0	0
Perioral numbness	0	0
Metallic taste	0	1 (5%)
Nausea	0	0
Twitching	0	5
Hives	1 (5%)	0

Data presented as n (%)

age duration was increased by surgeries other than endoscopic carpal tunnel release, such as Dupuytren's contracture excisions involving multiple digits.

There was a wide range in number of sites blocked at both five and ten minutes for each treatment group but there were no significant differences between groups, despite a power of 0.86-0.99 to detect a 25% difference. A number of patients had pain at the time of incision, despite a blunt pinprick sensation. There were no differences between groups in supplemental analgesia required, although five patients in the lidocaine group required 500 µg alfentanil for supplementation and two in the chloroprocaine group received 1000 µg.

The number of patients with a given muscle blocked increased between five and ten minutes, but there was no difference between treatment groups. Few side effects were detected for either group on tourniquet release. One patient in the lidocaine group had slight twitching of the operative arm only. In the CP group, one patient was slightly lightheaded, one patient had nausea, and one patient developed hives on the operative arm (Table IV).

Discussion

Chloroprocaine showed no clinical benefit over lidocaine for IVRA during short duration outpatient hand surgery. There was no difference in the speed of onset of sensory or motor block compared to lidocaine.

Although VAS scores were similar, the plain chloroprocaine group required more supplemental opioid than did the lidocaine group. Despite blunting of sensation to pinprick, some patients still complained of incisional discomfort. No patient experienced tourniquet pain requiring opioid in either group, which is not unexpected since the mean tourniquet time did not exceed 32 min in either study.

In addition, there was a higher incidence of metallic taste and hives and a non-significant trend towards more CNS side effects in the plain chloroprocaine group. The supplemental analgesia was changed from fentanyl to alfentanil in the second part of the study to take advantage of the faster onset and offset of alfentanil for outpatient surgery. It is unlikely that the choice of fentanyl *vs* alfentanil affected the incidence of nausea, dizziness or lightheadedness, as there was no difference in those symptoms between the lidocaine and chloroprocaine groups in either study. In a double-blind, randomized study of patients scheduled for minor hand surgery under chloroprocaine or prilocalcaine IVRA, an increase in heart rate of 20% occurred in three patients in the chloroprocaine group.⁹ Another evaluation of chloroprocaine *vs* prilocalcaine for IVRA resulted in four of ten volunteers in the chloroprocaine group developing an increase in heart rate greater than 20%, and one having short periods of junctional rhythm in the first two minutes after tourniquet deflation ($P < 0.05$).¹⁰ When comparing chloroprocaine with prilocalcaine for IVRA, it is important to note that the same dose of prilocalcaine results in considerably lower blood concentrations than lidocaine, the control drug used in our study.¹¹

These findings contrast with Korzeniewski *et al.*¹² who reported a lower incidence of CNS side effects with plain chloroprocaine than with lidocaine 0.5%. This may have been due to the relatively high doses (3.5 mg·kg⁻¹) in Korzeniewski's study of chloroprocaine (total dose 253 - 269 mg) and lidocaine (260 - 290 mg). None of our patients received > 200 mg of either agent. In a study by Palas, there were no signs of central nervous system toxicity in any of 30 patients given 60 mL chloroprocaine 0.5% for IVRA of the lower extremity.⁴ In comparison, six of 30 patients given 60 mL lidocaine 0.5% experienced CNS symptoms upon tourniquet release.⁴ Of note, 300 mg lidocaine would be greater than the recommended limit of 3 mg·kg⁻¹ lidocaine for IVRA¹ in most patients. When unanesthetized volunteers received intravenous infusions of local anesthetics, chloroprocaine was tolerated best, with the low toxicity considered to be due to its rapid hydrolysis by plasma cholinesterase, and lidocaine was the most poorly tolerated of the local anes-

thetics infused.¹³ Since plasma cholinesterase hydrolyzes only the ester-type local anesthetic agents, chloroprocaine should be avoided in patients with atypical plasma cholinesterase.¹⁴ The metabolic products of ester local anesthetics include the aminobenzoic acids, which may result in an allergic reaction in the sensitized patient.¹⁵

Although thrombophlebitis was not defined in the original clinical reports, Harris *et al.* noted that approximately 8% (four of 51) patients receiving chloroprocaine for IVRA developed thrombophlebitis at the site of the injection.¹⁶ There were no other risk factors in their patients for thrombophlebitis and there was no follow-up for morbidity. Dickler *et al.* did not report the incidence of thrombophlebitis in their patients, but stated that it did occur and subsided uneventfully in three of the cases which were followed.³ Thrombophlebitis was attributed to low pH, the preservative methylparaben, and the antioxidant sodium bisulphite.

In rabbits undergoing IVRA with 2-chloroprocaine 0.5% for 120 min, there was no thrombus formation or inflammatory changes observed during histologic or immunocytochemical examination.¹⁷ However, electron microscopy revealed damage of the venous endothelium in six of eight rabbit vein samples.¹⁷ Six of 38 of our patients receiving chloroprocaine developed short-lived hives on the operative arm with no evidence of systemic allergy or thrombophlebitis. Venous irritation and/or urticaria in the test arm after tourniquet release was observed in ten of 30 patients receiving 2-chloroprocaine compared with two of 30 patients receiving prilocaine 0.5% ($P < 0.05$)⁹ and in six of ten volunteers receiving chloroprocaine for IVRA.¹⁰ None of Korzeniewski's 26 patients who received IVRA with 3.5 mg·kg⁻¹ chloroprocaine 0.5% reported thrombophlebitis when contacted by telephone in follow-up,¹² nor did any of Palas' 30 patients who received 60 ml chloroprocaine 0.5% for IVRA of the lower extremity.⁴ A preservative- and antioxidant-free form of chloroprocaine 0.5% has been used extensively for IVRA for over four years in 84 hospitals in Switzerland and there have been no complaints to the manufacturer and no findings of thrombophlebitis.¹⁸ The importance of venous irritation and hives is unknown, but they do not seem to be related to clinical thrombophlebitis in humans.

Delivery of local anesthetic to the site of action depends in part on the agent's lipid solubility. The proportion of the lipid-soluble, uncharged free-base increases with increasing pH. Alkalinization with sodium bicarbonate shifts the equilibrium, resulting in a greater proportion of non-ionized free-base, and increasing the

concentration gradient of diffusible drug and drug transfer.¹⁹ This should result in a shortened time to onset of action. This effect has been demonstrated in epidural anesthesia using 2-chloroprocaine^{20,21} and lidocaine.²² In ten volunteers, alkalinization of prilocaine for IVRA decreased the time of onset of sensory and motor block, and slowed the time to recovery following tourniquet deflation.⁵ A clinical study using alkalinized prilocaine demonstrated less pain on injection, during surgery, and five minutes after tourniquet deflation, compared with plain prilocaine.⁶ In contrast Benlabed *et al.* were unable to demonstrate any difference with respect to loss of pin-prick sensation or time to maximum motor blockade using pH adjusted lidocaine 0.5% *vs* plain lidocaine.⁷ Similarly, there was no difference between alkalinized 2-chloroprocaine and lidocaine in speed of onset of either sensory or motor blockade in our study. The reason for this is unclear. Perhaps local acidosis secondary to tissue ischemia counteracts the effect of alkalinization, or conversely, any derived anesthetic effect due to cuff ischemia and acidosis is countered by relative local alkalinity. In addition, pH adjustment to 7.6 may yield a suboptimal concentration gradient for the lipid-soluble free-base, as the pKa of chloroprocaine is 8.9.²³ It is difficult to raise the pH of 2-chloroprocaine higher than 7.6 since it precipitates at pH 8.0.²⁴

Increasing the quantity of lipid soluble base form is not dependent only on increasing the pH of the local anesthetic but may also be achieved by decreasing the pKa of the drug or by increasing its concentration at the site. Warming the solution prior to injection may decrease the pKa. No specific effort was made to keep the solution temperatures the same, but all were at room temperature. Concentrations of chloroprocaine higher than 0.5% have been used, which may indeed speed onset, but these higher concentrations have been associated with a higher incidence of CNS side effects.²⁵ In addition, there is a concern of direct neurotoxicity with increased concentrations of local anesthetics.

The concentration of 0.5% was chosen as the test concentration for lidocaine and 2-chloroprocaine even though the difference in relative potency of lidocaine:chloroprocaine is approximately 2:1.¹⁵ This refers to the concentration required for an equivalent depth of block in humans and it is not known if this relationship can be extrapolated to IVRA.¹⁵ It is possible that the difference in relative potency may have influenced the results; however, the concentrations used represent the standard concentrations for IVRA in the recent literature.^{4,9,18}

Perhaps the most clinically intriguing result is the reduced incidence of CNS side effects and hives with pH adjustment of the chloroprocaine. This may have

been due to a higher tissue penetration of the lipid soluble base resulting in less availability for venous redistribution on tourniquet release. There were also fewer side effects in the lidocaine group in the second study. These differences may be related to the longer tourniquet times, although many of the procedures had inflation times similar to those in the first study. A minimum of 20 min is often advocated after the injection of lidocaine before deflation of the cuff,¹ but without any direct evidence to the contrary, it is recommended by Holmes that the cuff remain inflated for a minimum of 15 min.²⁶ None of the patients in either study had a tourniquet time of less than 15 min. It would be interesting to see if pH-adjusted 2-chloroprocaine offered an advantage over lidocaine or plain chloroprocaine in certain clinical situations of short tourniquet duration.

In conclusion, 40 mL of either plain or pH-adjusted 2-chloroprocaine 0.5% gave reliable anesthesia for IVRA in hand surgery, but had no clinical advantage over lidocaine 0.5% with respect to speed of block onset or motor block achieved. There was a higher incidence of side effects and need for supplemental opioids in patients who received plain chloroprocaine. Further investigations are required to confirm whether pH adjusted 2-chloroprocaine is beneficial in situations of short tourniquet duration and to ascertain the clinical importance of chloroprocaine-associated hives.

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