Original Research Article

Efficacy and duration of analgesia from a sustained-release lidocaine sheet in humans

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A b s t r a c t

We have synthesized a sustained-release lidocaine sheet (SRLS) and injectable sustained-release lidocaine particles (SRLP) using biodegradable polymers. In the present study, we performed an exploratory first clinical trial of the SRLS in healthy volunteers as a prelude to patient administration. This trial is meant as an initial intervention in ultimately developing and refining the SRLP.

We evaluated the intensity and duration of analgesia of the SRLS compared with 8% lidocaine spray. In Protocol 1, we applied the SRLS piece to the mucous membrane of the nasal vestibule. We examined the local pain threshold over 72 h after administration, and removed the SRLS after 72 h. Individuals that finished Protocol 1 underwent Protocol 2, in which we applied 8% lidocaine spray.

Twelve volunteers were enrolled and seven of these volunteers finished Protocol 1. All seven individuals who completed Protocol 1 also completed Protocol 2. The mean pain thresholds were 32 g, 78 g, 90 g, 90 g, 87 g, and 87 g at pre-administration and 4 h, 10 h, 24 h, 48 h, and 72 h after administration, respectively, in Protocol 1, and 36 g, 85 g, 49 g, and 33 g at pre-administration and 15 min, 2 h, and 4 h, respectively, in Protocol 2.

A sustained-release lidocaine using biodegradable polymers was applied as a sheet in humans for the first time in the world. It maintained significant analgesia for 72 h without major toxicities. Furthermore, degree of analgesia provided by the SRLS throughout the entire study was similar to that provided by the 8% lidocaine spray. It may suitable for management of postoperative pain especially in outpatients.

Keywords: sustained-release lidocaine, 8% lidocaine spray, biodegradable polymer, healthy volunteer, clinical trial, postoperative analgesia

Introduction

Appropriate postsurgical pain management contributes to improved healing, faster patient mobilization, shortened hospital stays, reduced healthcare costs, and increased patient satisfaction [1-4]. Additionally, aggressive management of acute postoperative pain by pre-emptive and multimodal analgesia may reduce the incidence of chronic postoperative pain [5-6].

Sustained-release local anesthetics may provide long-acting postoperative analgesia through a single administration at a surgical wound, around a nerve innervating the operation site or into epidural space without a continuous infusion catheter. Such a strategy could become an important addition to current multimodal approaches to postsurgical pain management by reducing the consumption of supplemental analgesics including opioids-related or continuous infusion catheter-related complications such as infection, bleeding, and compartment syndrome. Sustained-release versions of various local anesthetics have been produced in various forms [7-9] in particular, prolonged analgesic effects in animals [10-17] and humans [18-20] have been reported for sustained-release bupivacaine. Lidocaine is widely used as a local anesthetic because it has a wide safety margin for cardiac toxicity. Several sustained-release lidocaine formulations have already been produced [21-22] and the anesthetic effects of sciatic nerve block [23-25], epidural block [26,27], or local analgesia[28] by sustained-release lidocaine have been examined in healthy animals.

We have synthesized a sustained-release lidocaine sheet (SRLS)using biodegradable polymers, and we previously demonstrated the safety and efficacy of the SRLS for sciatic nerve block in a rat model of postoperative pain [29]. Furthermore, we have also synthesized injectable sustained-release lidocaine particles (SRLP), that are not sheets, from the same biodegradable polymers used for the SRLS, and we demonstrated that epidural injection of these particles produced prolonged anti-hypersensitivity in a rat model of postoperative pain with no major complications [17]. In the present study, we performed an exploratory first clinical trial for the SRLS in healthy volunteers prior to administration of the SRLS to patients. This trial is meant as an initial intervention in

Materials and methods

This study was approved by the institutional review board of Gunma University Hospital and registered with the University Hospital Medical Information Network (UMIN000008248, UMIN000009915). Written informed consent was obtained from all volunteers before enrollment. The aim of this clinical trial was to evaluate the duration and intensity of analgesia and the safety of the SRLS in the normal mucous membrane of healthy volunteers.

Subjects

The volunteers in this study were selected from the public and were compensated for damages with accident insurance. All volunteers were paid for their participation. All volunteers had medical records at Gunma University Hospital and were screened within 30 days prior to the start of administration. Healthy males aged 20 to 40 years were eligible to participate in this study. Subjects were excluded from participation if they had any diseases of the nasal cavities, allergies to amide-type local anesthetics, arrhythmia, or difficulty communicating, or if they had consumed any medications within 1 week of the start of the study. Individuals who were considered to be inappropriate for this study by a physician for any other reason were also excluded. The volunteers interviewed regarding their medical history and underwent a blood examination to determine the hemoglobin concentration and blood cell counts for white blood cells and platelets. The blood samples were also subjected to biochemical examination for total protein (TP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, Na, K, and Cl levels. The volunteers also underwent resting 12-lead electrocardiography (ECG).

Preparation of the study drug

We prepared SRLS loaded with 40% (w/w) lidocaine for this clinical study. We dissolved lidocaine (804.1mg; lidocaine powder; Sigma-Aldrich Corporation, St. Louis, MO) and PLGA (1,204mg; 50:50 poly (DL-lactide-co-glycolide) ester-terminated polymer;inherent viscosity, 0.55-0.75;Durect Corporation, Cupertino, CA,USA) in chloroform (6.310ml; 99.5%;containing 100-200ppm amylenes as a stabilizer; 1.492g/mL at 25 C; Sigma-Aldrich Corporation, St. Louis, MO,USA), and then poured the lidocaine/PLGA/chloroform solution into Petri dishes (inner diameter 48mm, area approximately 7616mm^2). The solutions were then desiccated for 2 days at 25 C in a class II, type A2 biological safety cabinet (Thermo Fisher Scientific Inc., Waltham, MA, USA) whose interior had been sterilized with a germicidal light, followed by1 week at 37 C in a vacuum-drying oven (Advantec Toyo Kaisha, Ltd Bunkyo, Tokyo, Japan)to allow the chloroform to completely evaporate. The drying converted the solutions to sheets, which were removed from the dishes and cut into pieces of approximately1cm 1cm, each

weighing approximately 50mg and containing approximately 20 mg of lidocaine. The prepared SRLS samples were then frozen and stored until use.

We determined the capacity of the SRLS to release lidocaine in vitro before the study. SRLS samples were placed into a vessel filled with 50mL of phosphate buffer (pH 7.40) prepared from monobasic sodium phosphate (12.69g) and dibasic sodium phosphate (43.74g) in 4L of distilled water. We prepared four vessels in the same way and sampled 0.5ml of the buffer from each of the vessels at several time points. The vessels were placed in a 37 C incubator except when sampled. The lidocaine concentration in each sample was measured by SRL Inc. (Shinjuku, Tokyo, Japan) using an enzyme immunoassay (EIA).

Evaluation of pain thresholds

The pain threshold was measured using anelectronic Von Frey anesthesiometer (IITC Life Science Inc., Woodland Hills, CA, USA). The polypropylene tip of the anesthesiometer was applied perpendicularly to the test site with a gradual increase in pressure by the subject, which released it from the site by himself in eliciting pain. The force needed to elicit pain was automatically recorded as a threshold in grams by the pressure transducer of the anesthesiometer.

Study Protocol 1

After measuring the pre-administration pain threshold, we applied a 50 mg SRLS piece (estimated to contain 20 mg of lidocaine) to one side of thenasal vestibule, and then fixed it in place using a ball of cotton wool (Figure 1).When the SRLS was applied, it was applied dry because it was expected to be wetted by the nasal mucus. To prevent the lidocaine from being released through the ball of cotton wool into the nasal cavity, one side of the sheet (the side not exposed to the nasal mucosa) was coated with a transparent thin polyurethane film using an acrylic adhesive (Tegaderm ™, Sumitomo 3M Limited, Shinagawa, Tokyo, Japan). The SRLS and the cotton wool were temporarily removed in every examination of the local pain threshold, and then the SRLS was placed back in its original position with a new cotton ball. We examined the local pain threshold and observed the administered site at 4 h, 10 h, 24 h, 48 h, and 72h after administration. The SRLS was removed after 72 h. We also performed medical interviews or examinations as needed during the application. All subjects underwent observation of the administered site, a medical interview or examination, and a blood examinations at one week after administration to detect serious side effects such as liver injury, renal injury, or pancytopenia. Bathing or exercise that could wet the ball of cotton wool in the nasal cavity was prohibited during the study (Table 1).

The sustained-release lidocaine sheet (SRLS) was applied to one side of the nasal vestibule (Protocol 1). The figures show a front view (left) and a side view (right) illustrating the right nasal cavity.
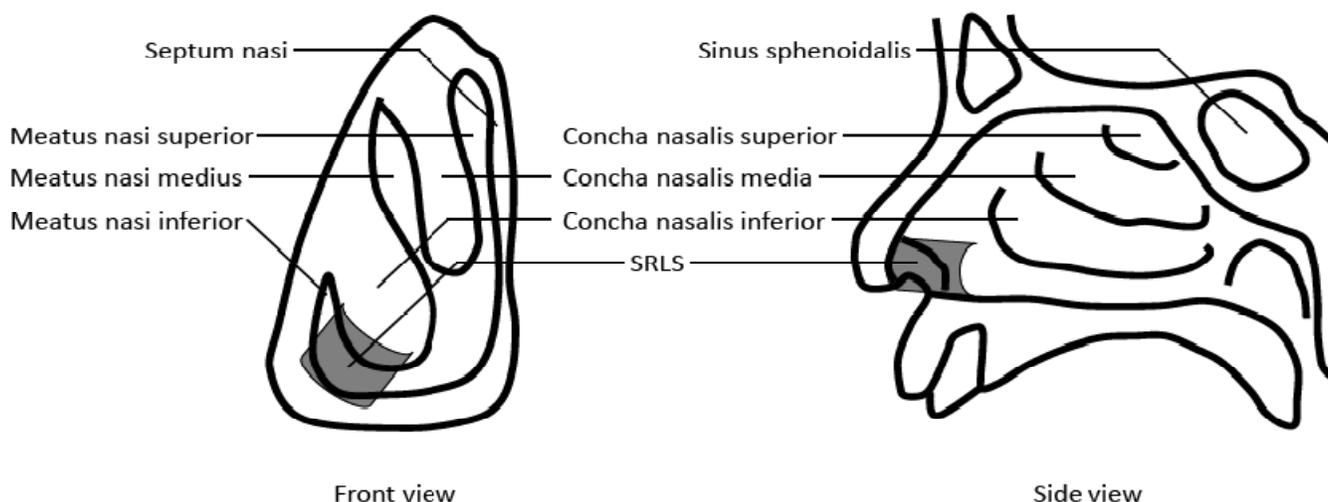
Figure 1: The position of the SRLS applied

Table 1: Timetable of Protocol 1

	Pre-	4 h	10 h	24 h	48 h	72 h	1 w
Pain threshold	o	o	o	o	o	o	
Observation of local site		o	o	o	o	o	o
Medical interview/examination	When needed						o
Blood examination							o

Study Protocol 2

Individuals that finished Protocol 1underwentProtocol 2 after at least one month had passed. In Protocol 2, after measuring the pre-administration pain threshold, we applied three pumps (estimated to contain 24 mg of lidocaine) of a 8% lidocaine spray (Xylocaine® pump spray 8%, AstraZeneca K.K., Osaka, Japan), a local anesthetic in current clinical use, to the same side of the nasal vestibule that had previously received the SRLS. We examined the local pain threshold at 15min, 2 h, and 4h after administration as described above. We performed medical interviews and examinations as needed but did not perform the blood examination after administration of the lidocaine spray. Because the duration of the effect of the lidocaine spray was expected to be short, we measured the pain thresholds at shorter time points than in Protocol 1 (Table 2).

Table 2. Timetable of Protocol 2

	Pre-	15 min	2 h	4 h
Pain threshold	o	o	o	o
Observation of local site		o	o	o
Medical interview/examination	When needed			
Blood examinations				

Statistical Analysis

The population in which safety was confirmed included all subjects who received the SRLS. The population used for the efficacy analyses thus included all subjects who received the SRLS and who underwent at least one pain threshold measurement after administration.

The pain threshold at each time point was compared with the pre-administration value using a two-sided paired t-test. The value for each blood examination parameter at one week was also compared with the pre-administration value using a two-sided paired t-test.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0). EZR is a modified version of R Commander (version 1.6-3) that adds statistical functions frequently used in biostatistics [30].

Results

The disposition of the volunteers is presented in Figure 2. Thirteen volunteers were screened, and 12 were enrolled. Seven of these volunteers finished Protocol 1; the other five volunteers discontinued the protocol 1(see Safety Assessment). All seven individuals who completed Protocol 1also completed Protocol 2. The mean age was 28 years (range, 23-34 years), and the mean weight was 62kg (range, 51-80kg). The mean (±standard deviation: SD) weight of the SRLS actually administered was 55.7 (±4.7) mg, the mean dose of applied lidocaine that was estimated to be in the SRLS was 20.0mg.
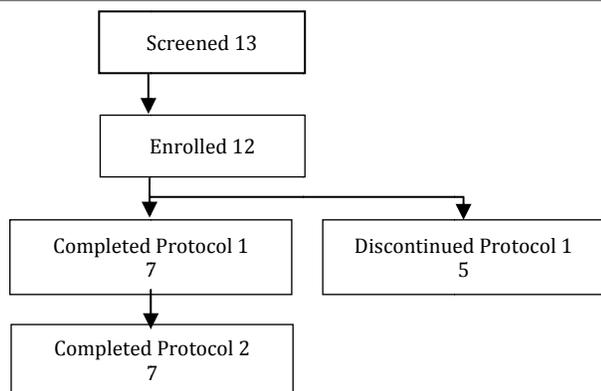
Figure 2: The disposition of the volunteers

Twelve subjects were enrolled. Seven of them finished Protocol 1, and the other five discontinued Protocol 1. The seven subjects who finished Protocol 1 all completed Protocol 2.

IN vitro release of licocaine from the SRLS

The cumulative release of lidocaine from the SRLS into phosphate buffer as a substitute for the nasal mucus was calculated. The SRLS showed approximately linear release of lidocaine over 4 d (more than the 72 h administration period in this clinical trial),with 34.1% released by 24 h, 60.9% released by 2 d, 74.8% released by 3 d and 86.1% released by 4 d (Figure 3).
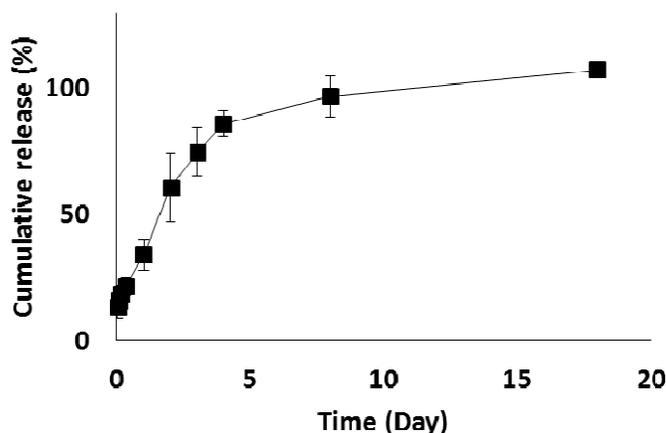

Figure 3: The cumulative release of lidocaine from the SRLS

Cumulative release of lidocaine from the sustained-release lidocaine sheet (SRLS) in phosphate buffered. The fraction of lidocaine released from the SRLS relative to the actual lidocaine content in the SRLS is shown as the mean±standard deviation (n= 4). The SRLS released lidocaine in an approximately linear manner for 4 d (more than the 72 h duration of the trial); 34.1% of the lidocaine was released within 24 h, 60.9% was released by 2 d,74.8% was released by 3 d, and 86.1% was released by 4 d.

Efficacy assessment

We assessed the efficacy of the SRLS by comparing the pain threshold at each time point after administration with the pre-

administration value (Figure 4). The mean (±SD) pain thresholds at pre-administration and 4 h, 10 h, 24 h, 48 h, and 72 h after SRLS administration were 32 g (±15), 78 g (±23), 90 g (±18), 90 g (±25), 87 g (±13), and 87 g (±17), respectively(Protocol 1).SRLS treatment significantly increased the mean pain threshold at all time points relative to the pre-administration value(P=0.000009, P = 0.000000009, P = 0.00001, P = 0.0000007, and P = 0.0006 respectively).

The mean (±SD) pain thresholds at pre-administration and 15 min, 2 h, and 4 h after administration of the 8% lidocaine were 36 g (±7), 85 g (±15), 49 g (±15), and 33 g (±5), respectively (Protocol 2). The 8% lidocaine spray treatment significantly increased the mean pain threshold relative to the pre-administration value, but only at 15 min after administration(P=0.0006).
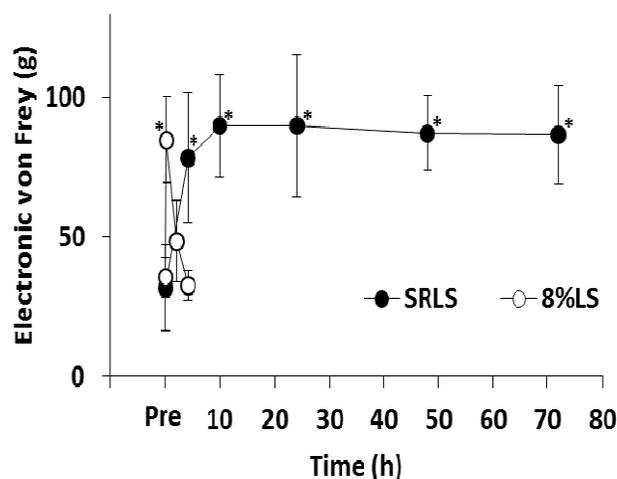

Figure 4: The pain threshold

Pain thresholds were determined using an electronic Von Frey anesthesiometer for groups of the sustained-release lidocaine sheet (SRLS) and the 8% lidocaine spray (8%LS). The pain thresholds were measured in g and are shown as the mean±standard deviation for each group. The mean pain thresholds were 32 g, 78 g, 90 g, 90 g, 87 g, and 87 g at pre-administration and 4 h, 10 h, 24 h, 48 h, and 72 h after administration, respectively, in Protocol 1 (SRLS), and 36 g, 85 g, 49 g, and 33 g at pre-administration and 15 min, 2 h, and 4 h, respectively, in Protocol 2 (8%LS).*P < 0.05 compared with the pre-administration value in each group.

Safety assessment

No subject reported symptoms of local anesthetic toxicity.

Five of 12 subjects who received the SRLS discontinued Protocol 1. In two of these subjects, the SRLS was removed for bathing by mistake or the SRLS came off while sleeping at night. In three of these subjects, the following three non-specific complications occurred; one case of nosebleed that may have been caused by a strong sneeze, one case of purulent rhinorrhea that may have been caused by a common cold, and one case of severe pain around the

nose that may have been caused by the use of a ball of cotton wool that was too large.

While two subjects finished Protocol 1, one experienced hypoesthesia in the tongue in the morning because post-nasal drip carried the lidocaine from the nose to the throat when the subject was sleeping at night. One subject also present a slight increase in liver enzyme activity (AST 40 IU/L, ALT 46 IU/L) and K levels (5.1 mEq/L) after administration, although this increase may have been caused by hemolysis when the blood was drawn. These parameters had returned to normal levels (AST 27IU/L, ALT 40IU/L, and K 4.4mEq/L) at the blood examination one week later. Overall, no clinically obvious meaningful shifts were noted in any of the chemistry or hematology values from screening. Almost all of the subjects experienced reactive serous rhinorrhea.

Discussion

In the present study, we demonstrated efficacy and safety of the sustained-release lidocaine sheet (SRLS) for providing analgesia to the normal mucous membrane of human volunteers. The SRLS significantly increased the mean pain threshold relative to the pre-administration for the entire 72 h duration of the study, but the 8% lidocaine spray was only effective for 15 min after administration. Furthermore, the extent of analgesia throughout the study in the SRLS-treated group was similar to that observed at 15 min inthe 8% lidocaine spray. Therefore, the efficacy of the SRLS was as high as that of the 8% lidocaine spray (the highest concentration in current clinical use) and maintained for 72 h. We did not examine the effect of the SRLS after 72 h because of the burden to the volunteers. However, we consider that the analgesic effect of the SRLS would likely last longer than 72 h because we previous observed an SRLS-mediated analgesic effect for 7 days after sciatic nerve block in a rat model of postoperative pain.[29] The in vitro data also supported this statement, as 25.2 % of lidocaine was still remaining in the SRLS after 72 h.

Although several complications occurred in this study, we considered that all of these complications were not related to SRLS; rather, they resulted from the study design, procedural complications or accidental complications in the study. Almost all of the subjects experienced reactive serous, which is not adverse but normal reaction in the nasal cavities. No subject reported symptoms of local anesthetic toxicity, although we did not measure the blood concentration of lidocaine in this study to reduce the burden on the volunteers. The mean dose of applied lidocaine that was estimated to be in the SRLS was 20.0 mg, which represents a common local anesthetic dose or dose for intravenous injection. Furthermore, the amount of lidocaine actually absorbed was less than 20.0 mg because the in vitro data showed that 25.2% of lidocaine was still remaining in the SRLS after 72 h.

The SRLS and 8% lidocaine spray treatment effectively increased the mean pain threshold but did not produce complete local anesthesia, which suggests that the lidocaine did not reach the submucous tissue from mucous membrane. Although SRLS was equally effective to the 8% lidocaine spray in current clinical use, surface anesthesia is not our final aim for the clinical use of SRLS.

Rather, our goal is to provide simple and effective postoperative analgesia with few side effects after a single administration of the sustained-release lidocaine particles (SRLP) around sensory nerves or into the epidural space, and to this end, we intentionally synthesized injectable SRLP from the same biodegradable polymers used for the SRLS so that it would be completely disintegrated and metabolized after administration. However, prior to clinical application of the SRLP, it was necessary to demonstrate the safety and efficacy of the SRLS, because we cannot easily remove the SRLP injected around sensory nerves or into the epidural space in an emergency. We chose to apply the SRLS to mucous membranes because they are easily accessible and allow easy removal of the SRLS in an emergency of the study. In particular, we chose the nasal mucous membrane because it is the most easily accessible among various mucous membranes.

A sustained-release lidocaine using biodegradable polymers was applied as a sheet in humans for the first time in the world. We designed this study for the main purpose of demonstrating no major toxicity, the sample was therefore limited to the minimum size and male for an exploratory first clinical trial in humans, which was not randomized, controlled, and blinded trial. A large-size full placebo-controlled study or dose-response study is necessary as the next step in the clinical introduction of the SRLS to demonstrate true safety and efficacy, for example, for skin pain form heat burns or shingles.

Epidural analgesia via an indwelling catheter is widely used for postoperative pain management. However, patients are increasingly treated perioperatively with anticoagulants or antiplatelets. Therefore, the invasive analgesic approach is now often replaced by continuous administration of opioids as in intravenous patient-controlled analgesia (IV-PCA) for management of postoperative pain to prevent neuroparalysis arising from the bleeding. However, the systemic administration of opioid analgesics is not always favorable because of side effects such as nausea, vomiting, sedation, respiratory depression, pruritus, constipation, and urinary retention. On the other hand, ultrasound guided peripheral nerve blocks are recently preferred for postoperative pain management because it is a relatively safety method for patients treated perioperatively with anticoagulants or antiplatelets. For getting long acting, these methods need continuous administration of local anesthetics using an indwelling catheter. Decreasing the risk of opioids-related adverse events without a continuous infusion catheter is particularly desirable in the outpatient setting; therefore, new postoperative analgesic methods are necessary. Not only outpatients but also inpatients may be promised long acting analgesia for postoperative pain without adverse events by wound local anesthesia, peripheral nerve block or epidural analgesia through a single injection of slow-release local anesthetics.

Conclusions

We demonstrated that an SRLS applied to the normal mucous membrane in the nasal cavity produced analgesia for at least 72 h without major toxicities. The intensity of the effect was comparable

with that of 8% spray lidocaine treatment. Postsurgical pain is most intense within the first few days after surgery; therefore, a sustained-release lidocaine using biodegradable polymers including the SRLS maybe suitable for management of postoperative pain.

Authors' Contributions

TS carried out the studies, performed the statistical analysis, and drafted the manuscript. MT participated in the design and coordination of the study and helped to analyze the data and draft the manuscript. HO participated in the design and helped to draft the manuscript.YT helped to prepare the study drug.SS conceived of the study, participated in its design, and helped to draft the manuscript. All authors have seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

Acknowledgments

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