Neurocrit Care (2019) 31:399–405
https://doi.org/10.1007/s12028-018-0659-9

NEUROCRITICAL CARE SOCIETY

REVIEW ARTICLE

Systematic Review of Intrathecal Nicardipine for the Treatment of Cerebral Vasospasm in Aneurysmal Subarachnoid Hemorrhage

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Abstract

Intrathecal nicardipine has been shown to have some efficacy for the treatment of symptomatic cerebral vasospasm in aneurysmal subarachnoid hemorrhage (aSAH). We performed a PRISMA-based systematic review of intrathecal nicardipine for the treatment of cerebral vasospasm in aneurysmal subarachnoid hemorrhage. A total of 825 articles were reviewed. After duplicates were removed and the search criteria was applied, 9 articles remained that were eligible for inclusion and analysis. 377 patients received a total of 6,596 injections of intrathecal nicardipine for aSAH-related cerebral vasospasm. The cumulative ventriculostomy-associated infection risk was 6%. Intrathecal nicardipine injections for aSAH-related cerebral vasospasm appears efficacious and safe. Administration of 4 mg of nicardipine every 12 hours was the most commonly reported dosing regimen. Intrathecal nicardipine decreases mean flow velocities on transcranial Doppler and reduces angiographic and clinical vasospasm. The infection risk appears to be in-line with studies in which rates of EVD-related infections have been reported.

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a disease that primarily affects adults between ages 40 and 60 with an incidence of approximately 10 per 100,000 people per year and a 30–50% mortality rate [1, 2]. Nearly 40% of these adults are unable to go back to work and even fewer are able to return to their previous occupations. The morbidity associated with aSAH often involves small, medium, and large vessel vasospasm leading to delayed cerebral ischemia (DCI) and subsequent stroke. These strokes vary in pattern from large wedge-shaped infarcts to smaller microvascular infarcts producing a wide variety of symptoms and sequelae.

Over 44 randomized control trials (RCTs) have been conducted in aSAH with 43 having a negative result for improvement in outcome [3, 4]. For the last three decades, the accepted treatment for small vessel vasospasm has been modified triple-H therapy: induced hypertension and hypervolemia. The best available treatment for large vessel vasospasm includes targeted intra-arterial therapy with calcium channel blockers (CCBs) and/or balloon angioplasty. In the real-world setting, patients often concomitantly exhibit small, medium, and large vessel vasospasm following aSAH and may have significant comorbid conditions, limiting the use of each treatment option for clinicians.

To maximize the efficacy of vasoactive medications and minimize their side effects, one must take into consideration the method of delivery. Multiple routes of administration that deliver CCBs to the central nervous system have been explored in the literature: intra-arterial injection and infusion, continuous intravenous infusion,

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surgically placed prolonged release implants, intrathecal injection, and continuous intrathecal infusion modalities [5, 6]. Each modality described above has risks and benefits and is used in varying degrees by clinicians. The ideal approach should treat vasospasm effectively, demonstrate adequate pharmacologic drug distribution throughout the cerebrospinal fluid (CSF), produce minimal side effects, engender fewer complications, and have bedside administration capability.

Intrathecal nicardipine has been shown in small retrospective and prospective studies to improve symptomatic vasospasm, improve outcome, decrease severe angiographic vasospasm, and decrease mean flow velocity [7–14]. In this paper, we present a systematic review of intrathecal nicardipine that will cover injection dosing regimens, effects on cerebral blood flow, side effects, treatment risks, patient selection, and outcome.

Methods: Search Strategy and Study Eligibility

An electronic search of the literature was performed using PubMed, Google Scholar, EBSCOhost, EMBASE, Scopus, and CINAHL in accordance with the PRISMA statement. The studies included in this review examined the use of nicardipine injected through an external ventricular or cisternal drain for the treatment of cerebral vasospasm related to aneurysmal subarachnoid hemorrhage. Search terms used in various combinations included: "vasospasm," "subarachnoid hemorrhage," "intrathecal," "intraventricular," "aneurysmal subarachnoid hemorrhage," "cerebral vasospasm," and "nicardipine." Eligibility for review was restricted to articles written in English or manuscripts with an adequate English translation. The following types of studies were found: retrospective chart reviews, observational studies, prospective observational studies, retrospective case control, and prospective non-randomized studies. No RCTs were found. Case reports were not included in this systematic review. No restrictions were made based on publication date. All included studies were published, peer-reviewed manuscripts with human subjects. After an initial search of the selected keywords was completed on PubMed, the studies that met the selection criteria were reviewed. Searches on subsequent databases were conducted in the same manner, and duplicates were removed. Data from the studies included: patient number, study type, subsequent development of ventriculitis/meningitis/central nervous system (CNS) infection, other complications, total number of doses administered, outcome, location of injection, and inclusion criteria. One reviewer (S.H.) conducted the search, which was verified by another reviewer (R.G.)

A total of 825 articles were reviewed. After duplicates were removed and the search criteria were applied, nine articles remained that were eligible for inclusion and analysis (Fig. 1). An initial search on the PubMed database with the terms "intraventricular nicardipine" and "aneurysmal subarachnoid hemorrhage" yielded 37 articles, of which eight were chosen. The next search combined the terms "intrathecal nicardipine" with "aneurysmal subarachnoid hemorrhage." It yielded 19 more articles, of which one was chosen. The terms "cerebral vasospasm" and "nicardipine" yielded 145 articles of which one was chosen. Next, the search was broadened to include as many articles as possible. The terms "vasospasm" and "nicardipine" yielded 379 articles. After duplicates were removed, 0 was chosen for review. Google Scholar yielded one new result after searching for "intraventricular nicardipine." Subsequent searches with Google Scholar, EBSCOhost, Scopus, CINAHL, and EMBASE databases yielded a total of 245 articles that were screened and ultimately deemed ineligible for inclusion.

Dosing Regimen and Drug Concentration

Multiple dosing regimens and preparations have been used in the administration of intrathecal nicardipine. Initial studies used 4 mg nicardipine diluted in 10 mL of 0.9% normal saline delivered through a cisternal drain [12, 13]. More recent studies have used the same dosage in a smaller dilution volume of 2 mL of 0.9% normal saline to minimize the volume injected intrathecally. Because the more recent series involved intraventricular administration via the external ventricular drain (EVD), one can speculate that a smaller dilution volume was used to decrease chemical irritation to the ependymal surface of the ventricles and maximize delivery. Goodson et al. [10] proposed a more concentrated preparation in which premixed nicardipine hydrochloride 4 mg/1.6 mL solution was mixed with preservative-free 0.4 mL sodium chloride to yield a total volume of 2 mL. Other reported dosages and frequencies have ranged from 2 to 4 mg every 6–12 h, the most commonly reported regimen being 4 mg every 12 h. Reported duration varies from as little as one to two injections during maximal cerebral vasospasm up to 10 days of treatment when administered in a prophylactic manner.

To date, only one clinical study has reported on the concentration of CCBs in CSF following intrathecal administration. After administering 4 mg of intrathecal nicardipine twice daily to 14 patients, Suzuki et al. tested trough samples obtained on post-bleed day nine. The authors reported a mean CSF concentration of 231.44 ng/mL and a serum concentration of 21.05 ng/mL [12]. These findings are within range of the median requisite CSF concentration reported by Yamamoto et al. [15] to elicit physiologic vasodilation in vitro. Given that

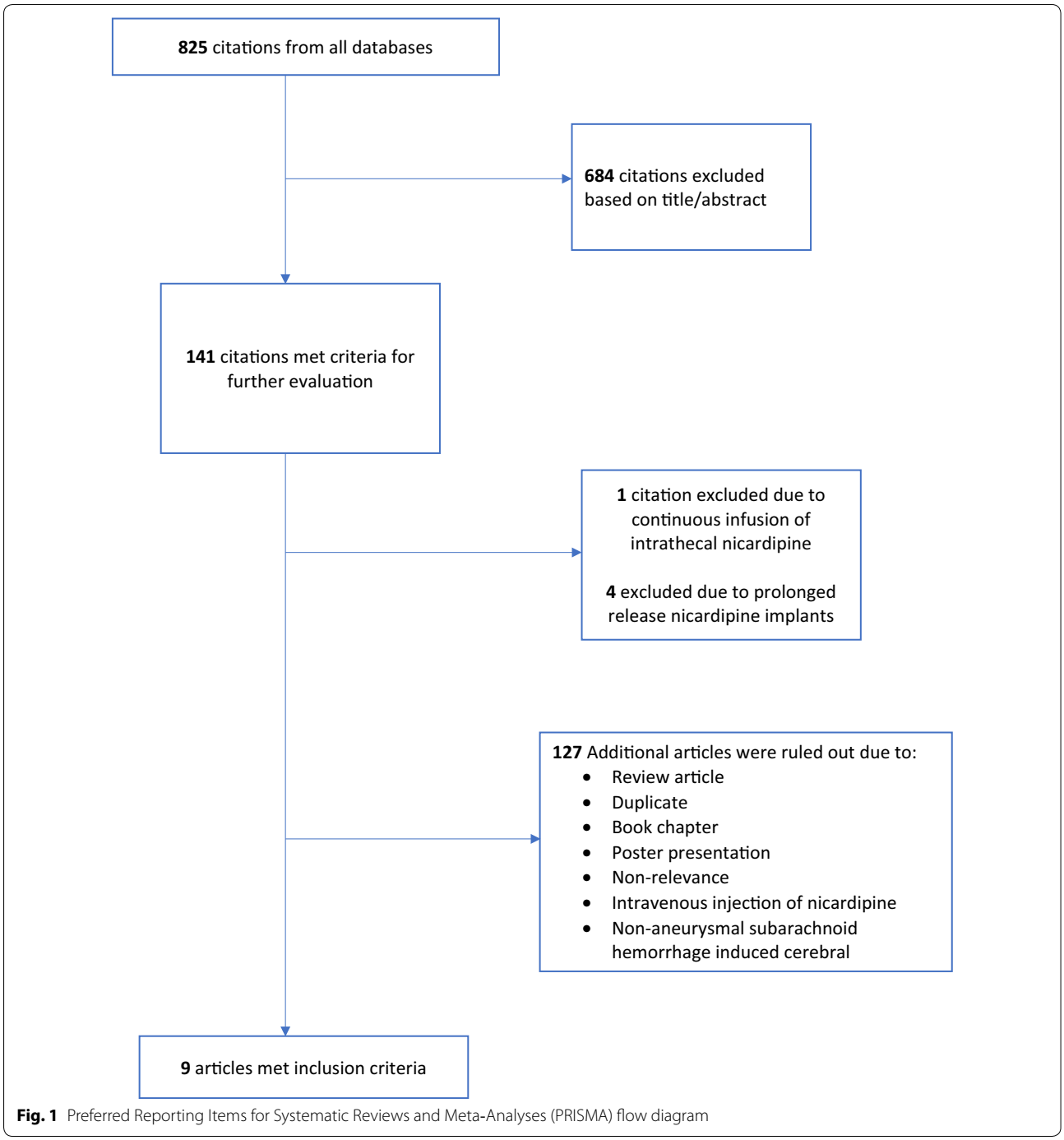

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

the protocol employed by Suzuki et al. [12] involved the administration of intrathecal nicardipine every 12 h, the requisite CSF concentration for vasodilation was likely maintained during the interval between each administration. Further study, examining how drug distribution within the CSF affects vascular and parenchymal targets is still needed to demonstrate the efficacy of intrathecal nicardipine in the treatment of aSAH.

Cerebral Blood Flow

Increased cerebral blood flow velocity is a hallmark of intracranial vasospasm that has been associated with DCI and worsened outcome. The detection, monitoring, prevention, and treatment of DCI are of paramount importance to the treatment of patients with aSAH. Initial pilot data obtained from SAH animal models demonstrated less vasoconstriction following the administration

of intracisternal nicardipine [16]. Pasqualin et al. [16] injected autologous blood into the cisterna magna of rabbits to elicit basilar artery vasoconstriction that was subsequently measured via diameter and luminal area. The authors compared seven rabbits that received a continuous infusion of intracisternal nicardipine after SAH to seven rabbits that had no intervention for SAH and seven control rabbits. The intracisternal nicardipine group was given 5.18 mg/10 mL at a rate of 12 μL/min for 120 min just prior to killing at 72 h post-SAH induction. The SAH group that did not receive any intervention exhibited significant basilar artery vasoconstriction: a 43% reduction in luminal area compared to the control group. The SAH group that received an infusion of intracisternal nicardipine demonstrated a 22% reduction in luminal area, indicating a significant vasodilatory effect of intracisternal nicardipine.

Human studies in which intrathecal nicardipine administration has been used for treatment of aSAH have evaluated cerebral blood flow through many different studies; however, we will focus on the two most common: transcranial doppler (TCD) mean flow velocity and diagnostic angiography. In most of the trials reported, TCD measurements occurred daily and intrathecal nicardipine was initiated when the middle cerebral artery (MCA) velocity was observed to be above 120 cm/s with or without clinical deterioration. Lu et al. [8] studied 14 patients and showed a mean pre-treatment right MCA velocity of 120 cm/s. In two of their patients, sonographic vasospasm resolved after two and five days of treatment; however, it recurred in seven of the other patients when intraventricular nicardipine administration ceased. Daily mean TCD values decreased after intraventricular nicardipine treatment to 82 cm/s across the cohort. In the Ehtisham et al. series of eight patients with severe vasospasm—as demonstrated by pre-treatment MCA velocities ranging between 135 and 276 cm/s—the authors reported a mean decrease of 43.1 cm/s in MCA velocities within 8 h of giving intraventricular nicardipine [9]. Finally, in the largest retrospective study examining TCD velocities after intrathecal nicardipine administration, Webb et al. [11] reported a reduction of mean MCA velocity from 155 to 129 cm/s post-treatment in 64 patients (see Table 1).

Among the studies that evaluated angiographic vasospasm rates, Suzuki and colleagues demonstrated postoperative angiographic vasospasm in 11.3% of their cohort who received a prophylactic 4 mg intracisternal nicardipine injection twice daily for 11 days [12]. The interval or timing of postoperative angiography was not disclosed. Shibuya et al. [13] showed a 26% reduction in symptomatic vasospasm and 20% reduction in angiographic vasospasm when 50 patients who prophylactically received intrathecal nicardipine were compared to 91 historical controls. The authors demonstrated this improvement by comparing preoperative angiograms to postoperative angiograms following aneurysm rupture performed at a mean of 12.3 days for the control group and 14.5 days for the intrathecal nicardipine group. Toyota et al. [14] noted an absolute reduction of 22% in the incidence of severe vasospasm among 21 patients who received intrathecal nicardipine twice daily for 10 days compared to controls (7% vs. 29%).

Table 1 Intraventricular nicardipine-related decrease in mean flow velocity measured by transcranial Doppler

Study	*N*	MCA Mean flow velocity reduction (cm/s)
Lu	14	− 38
Ehtisham	6	− 43
Webb	64	− 26.3

MCA middle cerebral artery

Infection Risk

A significant concern regarding the injection of medications into the intraventricular space is the potential risk for bacterial or chemical ventriculitis. Minimization of CSF sampling and EVD manipulation has been demonstrated to reduce risk of ventriculitis [17]. Thus, an appropriate consideration for the clinician is whether injection of intrathecal nicardipine could lead to increased incidence of infection in the CNS. Shibuya et al. prophylactically injected nicardipine three times per day into a cisternal drain placed during surgery in 50 patients with aSAH who underwent microsurgical clipping for an average of 10 days [13]. The incidence of meningitis in their cohort was 4%. Suzuki and colleagues similarly administered nicardipine prophylactically into cisternal drains following craniotomy for aneurysm clipping in 177 patients [12]. Their protocol involved twice daily injections for a total of 3894 injections. The authors reported an infection rate of 6.2%; 10 of the 11 infections were resolved with use of antibiotics. In these two studies, nicardipine was flushed along with 10 mL of saline upward of three times a day in patients who underwent open microsurgical clipping, which potentially increased their risk for infection. Thus, one may posit whether a standardized injection technique, drug dilution volume minimization to 2–4 mL, isovolumetric injection, and strict observation of sterile precautions could lead to further reduction in the observed rates of infection, especially given that the majority of patients undergo endovascular coil embolization in modern clinical practice.

The incidence of infection is significantly different when studies limit the administration of intrathecal nicardipine to patients who have only moderate–severe angiographic vasospasm or severely elevated TCD velocities, with or without clinical deterioration. Among six recent studies in which authors retrospectively analyzed an aggregate of 106 aSAH patients who received 903 total injections via EVD, zero CNS infections were reported. One contemporary outlier exists: Inoue et al. [18] retrospectively studied 26 patients and reported that six developed meningitis. However, the injection method was not disclosed and the authors did not include the proportion of cisternal injections to EVD injections. Fujiwara and colleagues prospectively studied five patients in which a continuous intrathecal infusion of 8 mg nicardipine was delivered daily over 14 days via cisternal drain with no patients developing infectious complications [5].

In total, 377 patients received 6595 intrathecal nicardipine injections in nine studies with a cumulative infection rate of 6% (see Table 2). Given that the rate of ventriculostomy-associated infections or ventriculostomy-related infections is estimated to be 8.8%, the cumulative infection rate observed among patients receiving intrathecal nicardipine via EVD or cisternal drain appears to be in line with that estimation [19]. Hanley et al. [20] support the notion that intraventricular administration of medication can be performed without increasing infectious complications for patients. The CLEAR III trial, for example, demonstrated that daily intraventricular injections of tissue plasminogen activator could be administered without a concomitant increased risk of infection. Strict implementation of sterile technique and protocols involving EVD placement, handling, and the standardization of intraventricular medication injection is critical to minimizing a patient's risk for infection during the delivery of intrathecal nicardipine in the setting of aSAH.

Patient Outcome and Selection

Overall, eight studies with 346 patients undergoing treatment with intrathecal nicardipine have demonstrated decreased angiographic vasospasm, decreased symptomatic vasospasm, and a reduction in mean flow velocity as measured by transcranial Doppler. Though the data supports the efficacy of intrathecal nicardipine in reducing the incidence of vasospasm following aSAH and, in turn, reducing disability, the different primary outcome measures, dosage, duration of therapy, and clear selection bias represent key limitations in conducting an extensive critical analysis of the literature.

In the 177 patients included in their study, Suzuki et al. [12] reported good recovery in 15 of the 20 patients who had vasospasm and 131 of 177 overall. Shibuya and colleagues [13] reported that the rate of good clinical outcome increased 15% among their 50 patients when compared to 91 historical controls. However, "good clinical outcome" was not specifically defined by the authors. As reported by Goodson [10], six out of eight patients with refractory vasospasm who were given intraventricular nicardipine were discharged home. Conversely, Lu et al. [8] did not report a difference in the modified Rankin Scores among 14 patients with refractory vasospasm at days 30 and 90. The discrepancy in the outcomes seen among these trials needs to be resolved with a well-planned RCT that addresses several questions: the safety of repeated nicardipine injections via EVD, its use as prophylactic or rescue treatment, whether it should be utilized in synergy with other treatment options, and finally,

Table 2 Reported studies of intraventricular nicardipine use in aneurysmal subarachnoid hemorrhage: size, type, complications, dose, location of CSF diversion, and total number of doses reported

Study	*N*	Type	IVT Infection	Other complications	Dose	Location	Total no. of doses
Ko	11	Retrospective	0	None	4 mg every 8–12 h	EVD	54
Lu	14	Retrospective case control	0	None	4 mg mean of 7 doses	EVD	111
Ehtisham	6	Retrospective	0	None	4 mg every 12 h	EVD	34
Goodson	8	Retrospective	0	Headache	4 mg every 12 h	EVD	153
Webb	64	Retrospective case control	4	None	4 mg every 8–12 h	EVD	429
Suzuki	177	Prospective observational	11	Higher incidence of VP shunting	4 mg every 12 h × 11 days	CCD	3894
Shibuya	50	Prospective, non-randomized	2	Headache	2 mg every 8 h × 10 days	CCD	1500
Toyota	21	Retrospective	Not reported	Not reported	4 mg every 12 h × 10 days	CCD	420
Inoue	26	Retrospective	6	Not reported	Not reported	CCD/EVD	Not reported
Total	377		23 (6%)				6595

CCD cisternal drain, *CSF* cerebrospinal fluid, *EVD* external ventricular drain, *IVT* intraventricular

whether the administration of IVT nicardipine leads to improved functional or cognitive outcomes.

Limitations

One of the limitations of our systematic review is the heterogeneity of the studies we examined. When analyzing outcomes among patients receiving intrathecal nicardipine outcome, measures were self-reported and sometimes did not include a control group for comparison. There is also a significant detection bias, or detection of effectiveness of the treatment, due to non-blinding and non-randomization. The primary outcome measures for each trial were also different: clinical outcome, reduction in TCD mean flow velocity, observed rates of angiographic vasospasm, or even discharge location. These biases could be resolved with a well-designed RCT.

Conclusion

Intrathecal nicardipine injections for the treatment and possible prevention of aSAH-related cerebral vasospasm appear efficacious and safe. Administration of 4 mg of nicardipine followed by 2 mL of saline flush with sterile precautions and isovolumetric technique every 12 h has been the most commonly reported dosing regimen. Intrathecal nicardipine decreases mean flow velocities on daily TCDs and reduces angiographic and clinical vasospasm in patients with cerebral vasospasm following aSAH. The overall number of infections observed in patients receiving this therapy appears to be in line with studies in which rates of EVD-related infections have been reported. A strict intrathecal medication administration protocol, including preparation and transport, should be instituted to include sterile technique, isovolemic CSF aspiration, and limitations on injection volume (we have included our institutional protocol for reference). It is unclear whether there is an improvement in functional or cognitive outcome or a reduction in delayed cerebral ischemia. The recent early termination of the NEWTON 2 trial of EG-1962—regarding the use of an EVD injection of a polymeric microparticle that slowly releases nimodipine over 21 days—was disappointing [21]. A well-designed industry-sponsored or National Institutes of Health funded RCT for intrathecal nicardipine therapy is the next logical step for this off-label therapy. A proposed study should help determine whether intrathecal nicardipine improves outcomes for patients with high-grade SAH who have radiographic, sonographic, or clinical signs of vasospasm. The study should include radiographic and clinical outcome measures and data regarding infection risk, long-term shunting rates, cerebral blood flow hemodynamics, and number of diagnostic cerebral angiograms.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s12028-018-0659-9) contains supplementary material, which is available to authorized users.

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Authors' Contributions
SH and RG contributed equally to the design of the study. SH performed the preliminary data analysis with confirmation by RG. SH and RG equally contributed to the analysis of the results and writing of the manuscript.

Source of Support
The authors received no support for this contribution.

Compliance with Ethical Standards

Conflict of interest
The authors declare that they have no conflict of interest.

Published online: 3 January 2019

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