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The Effect of Locally Administered Dexmedetomidine on Postoperative Pain in Patients Undergoing General Anesthesia for Perianal Surgery: A Comparative Randomized Clinical Trial

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Abstract

Background: Perianal surgery can cause a considerable amount of pain, which requires appropriable management.

Aim: This study was performed with aim to evaluate the effect of local dexmedetomidine administration on postoperative pain in patients undergoing general anesthesia for perianal surgery.

Method: This double-blind randomized clinical trial was conducted on patients undergoing general anesthesia for perianal surgery at Ghaem Hospital in Mashhad, Iran, between June 2020 and June 2020. Patients were randomly allocated to dexmedetomidine (DEX) or control groups. All patients underwent the same process for anesthesia. The patients in the DEX Group received a local injection of 1.5 µg/kg dexmedetomidine in 10ml of normal saline around the operation site at the end of the surgery and the control group did not receive any local injection. The primary outcome was post-operative pain scores in the first 24h after surgery.

Results: The DEX group exhibited significantly reduced pain scores at rest in 1, 3, 6, 12, and 24 hours after the surgery (p= 0.004, 0.010, 0.001, and 0.008, respectively). Furthermore, the pain scores in the DEX group were lower than the control group at the same time intervals after the operation (p=0.000, p=0.001, p=0.001, and p=0.015, respectively). The consumption of paracetamol and methadone was also significantly lower in the DEX group than in the control group at 3, 6, and 12 hours after surgery (p=0.010, p=0.003, and p=0.008, respectively).

Implications for Practice: Local perianal administration of dexmedetomidine reduces postoperative pain scores and analgesic consumption in patients undergoing general anesthesia for perianal surgery.

Keywords: Dexmedetomidine, General Anesthesia, Nausea and Vomiting, Perianal Surgery, Postoperative Pain

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Introduction

Proctological diseases, such as hemorrhoids, anal fissures, and anal fistulas are common colorectal issues accounting for about 5% of the general population, of which in about 10% of them surgery treatments are required (1, 2). An anal or anorectal fistula is a chronic inflammatory tract that connects the anal canal to the perianal skin (3). Dexmedetomidine is a highly selective alpha-2-adrenoreceptor agonist commonly administrated intravenously to provide sedation, anxiolysis, and analgesia (4). Dexmedetomidine has been also shown to have anti-hypertensive, anti-shivering, anti-nauseating, and sympatholytic properties, and reduce postoperative analgesic requirements (5, 6). Dexmedetomidine sedation has been linked to a variety of beneficial outcomes, including shorter periods of mechanical ventilation and intensive care unit (ICU) stay, a decreased likelihood of delirium, and improved cognitive function following surgery. Its analgesic properties have been recognized in various contexts, such as supplementing intravenous analgesics, enhancing peripheral nerve blocks, and augmenting intrathecal anesthesia. Wide-ranging benefits of Dexmedetomidine also include reducing postoperative nausea and vomiting, mitigating shivering, enhancing sleep quality, alleviating sore throat symptoms, and preventing discomfort related to catheters (7).

Although perianal surgeries are usually performed in a short stay, they can cause a significant amount of pain and discomfort (8). Therefore, adequate pain management is a crucial aspect of perianal surgeries. In most cases, general or regional anesthesia is used (9). Mepivacaine, bupivacaine, lidocaine as local anesthetics for perianal surgeries has been used and favorable results are reported (9). Choudhury et al. demonstrated that the use of a radiofrequency (RF) device for fistulotomy resulted in less postoperative pain and improved healing time, albeit with minor incontinence (10). Dexmedetomidine was suggested as a beneficial treatment following cardiac surgery because alleviates pain, reduces instances of delirium and arrhythmia, and possibly decreases the risk of immediate mortality (11). Most studies on dexmedetomidine have focused on its safety characteristics and the potential for administration via multiple routes. This has led to an increase in its various uses, particularly in pediatric patients, epidural labor analgesia, painful procedures, and as a premedication before surgery (7). Although there is limited research on dexmedetomidine, a significant impact of the effects of dexmedetomidine on the outcomes of critically ill patients has been reported. However, even with the introduction of multimodal analgesia and regional anesthetic techniques in clinical practice, postoperative pain management remains a challenge (12, 13).

To the best of our knowledge, no study has investigated the efficacy of local administration of dexmedetomidine as an individual local agent for patients undergoing general anesthesia for fistulotomy. Therefore, the present study was conducted with aim to evaluate the effect of local dexmedetomidine on postoperative pain in patients undergoing general anesthesia for perianal surgery.

Methods

This parallel double-blinded randomized clinical trial study was performed on 50 patients undergoing general anesthesia for perianal surgery at Ghaem hospital of Mashhad University of Medical Sciences (MUMS), Mashhad, Iran, between June 2020 to June 2020. The sample sized was calculated according to the data of the study by Waleed et al. (14), and considering alpha of 0.05 and a power of 90% based on the mean VAS score in the digits with RP, and a sample size of 25 subjects was determined in each group. The determination of the sample size was based on the anticipated number of participants needed to compare the means of two independent groups (15).

Participants were recruited among adults aged 18 to 60 years, with a physical status of American Society of Anesthesiologists (ASA) Grade I or II, scheduled for perianal surgery under general anesthesia. Exclusion criteria were diabetes with neuropathy, neuromuscular disease, psychological disease, drug addiction, pregnancy, morbid obesity (BMI>30 kg/m^2), perioperative heart rate lower than 45 B/min, and degree 2 and 3 atrioventricular block. Patients using blood pressure-lowering drugs such as Methyldopa, clonidine, and other alpha-2-adrenoreceptor agonists and analgesic or NSAID use in the past 24 hours were also excluded from the study. Prior approval was obtained from the Institutional Ethics Committee and all participants provided informed consent.

Patients who were candidates for perianal surgery were selected as the study participants from the available sample. The participants were randomly divided into two groups using the block permutation method. Each block was of the same size and there were 6 blocks. Each block included 3

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participants in the intervention group and 3 participants in the control group. To generate the random sequence, a specific software designed for random allocation was used. The sealed opaque envelopes were used to conceal the sequence. The intervention group received DEX, while the control group received standard treatment. Both the person responsible for data collection and the care provider were blind to group allocation and the type of intervention.

The demographic information, including age, gender, and weight was recorded for each patient. Then, all patients underwent the same procedure for anesthesia. Patients received oral alprazolam 0.5 mg the night before the surgery and 2 hours before starting the surgery. The patients received an intravenous infusion of 5 ml/kg/h lactated Ringer's solution before induction of general anesthesia. Anesthesia was induced using Fentanyl 2μg/kg, propofol 2–3 mg/kg intravenous (IV), midazolam 0.15 mg/kg IV, Atracurium 0.5 ml/kg IV. For the maintenance of anesthesia propofol, 100-150 μg/kg and isoflurane 0.6-0.8 MAC were used. Following the induction of anesthesia and establishment of neuromuscular blockade, oxygenation was typically achieved through intermittent positive pressure ventilation using a facemask. However, during tracheal intubation attempts, the facemask must be removed, resulting in a period in which no oxygen is supplied. In all patients, arterial blood pressure, electrocardiography, capnography (Etco2) and pulse oximetry were monitored.

For the patients in the DEX Group, 1.5 μg/kg of dexmedetomidine (PRECEDEX™, Hospira, Inc, Rocky Mont, USA) was locally injected (intramuscular) via a 24–25-gauge needle by anesthesiologist. The injection contained 10cc solution of dexmedetomidine and normal saline and was administered intramuscularly around the operation site at the end of the surgery. In the control group, normal saline serum was locally injected. All patients were observed for 24 hours after the operation. The primary outcome was to assess pain at rest using the visual analogue scale (VAS 0–10: 0=no pain, 10=worst imaginable pain) at 1, 3, 6, 12, 24 hours after surgery. The validity and reliability of this tool has been confirmed in several studies (16). Whenever VAS score was ≥4, 1mg of IV Paracetamol was administered and if the pain was not relieved, an additional 5 mg of methadone was given.

The number of patients requiring rescue analgesia and the amount of rescue analgesic consumption during the first 24 h after the surgery was recorded. The incidence of nausea and vomiting was assessed at 1, 3, 6, 12, 24 h after the surgery. The incidence of shivering was assessed at 3 and 12h after the surgery. Lastly, heart rate and blood pressure of all the patients were recorded before the surgery and at 1, 3, 6, 12, 24 h after the surgery.

Descriptive statistics were presented as means, standard deviations, and/or percentages. Prior to analyzing the data, the Shapiro-Wilk test was used to confirm the normality of the data. Qualitative data were compared using the Chi-Square test. In cases where the data were normally distributed, the independent sample t-test was used to compare quantitative data between the two groups. If the data were not normally distributed, the Mann-Whitney test was used. All data were analyzed using a specific statistical software (version 22, Chicago, IL, USA). $p<0.05$ was considered statistically significant.

Ethical Consideration

This study has received ethical approval from the research ethics committee of the Iran National Institute for medical research development (IR.MUMS.MEDICAL.REC.1399.355) and is registered in www.IRCT.ir (registration ID: IRCT20100920004780N11).

Results

Among the 238 eligible participants, 180 did not met the inclusion criteria and 8 had no consent to participate in the study. Finally, a total of 50 patients were recruited (25 in each group) (Figure 1).

The mean age of participants in the DEX group was 40.68 ± 10.64 years versus 42.36 ± 11.75 years in the control. Both groups were similar in terms of patient age, sex, weight, and, ASA physical status ($p> 0.05$) (Table. 1).

The mean pain scores of the patients in each group at 1, 3, 6, 12, and 24 h after the operation were reported in Table 2. The DEX group had significantly lower pain scores at 1, 3, 6, 12, and 24 h after the operation (p=0.004, 0.010, 0.001, and 0.008, respectively). The results revealed that the pain scores in the DEX group were lower than the control group at 1, 3, 6, 12, and 24 hours after the operation (p=0.000, 0.001, 0.001, and 0.015, respectively) (Table 3).

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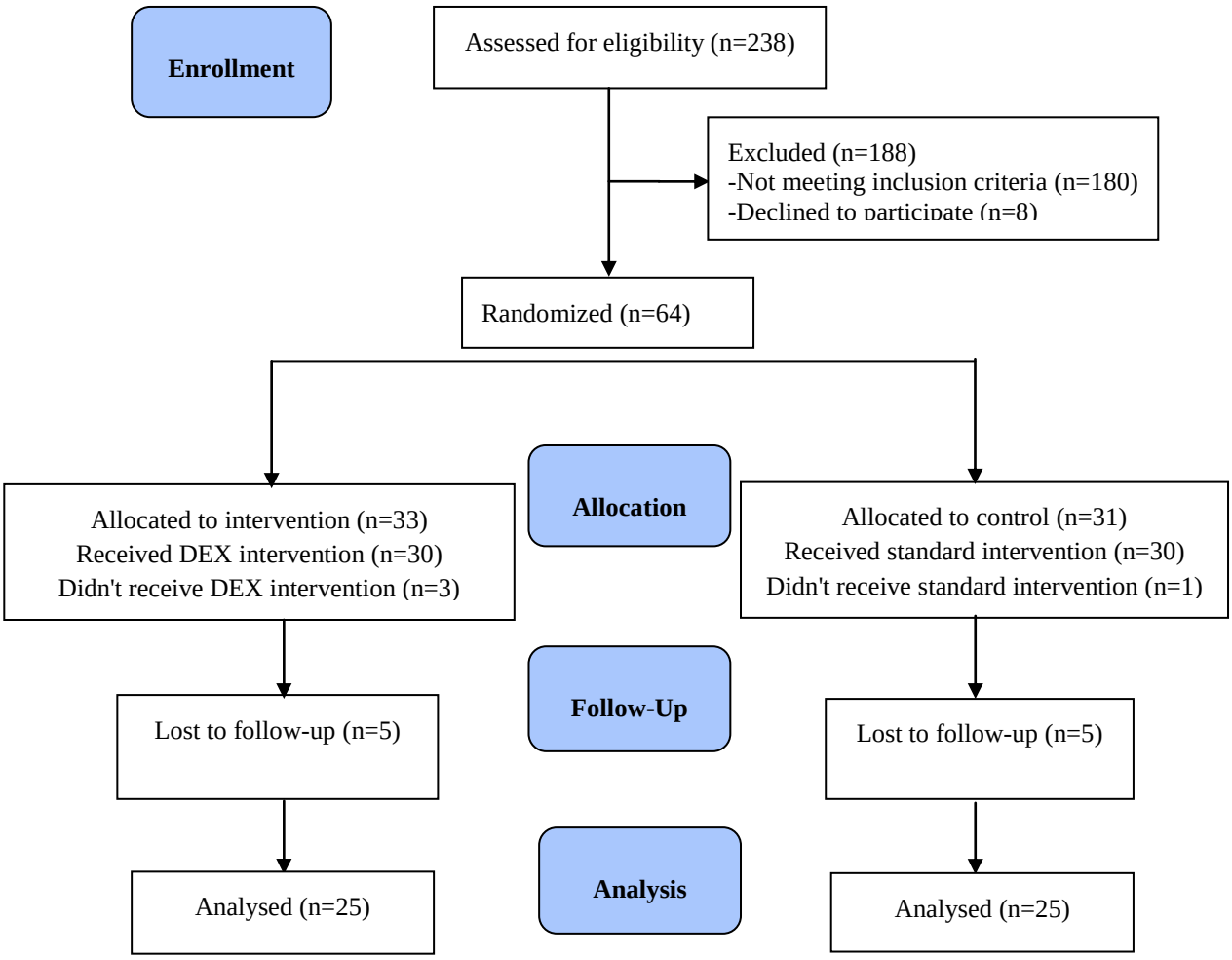

Figure 1. Flow diagram of the study process

There was no significant difference in terms of mean heart rate and mean blood pressure in the first 24 h after the surgery (Table 3). The DEX group had a significantly lower incidence of shivering as compared to the control group at 3h after the surgery (p<0.050), but there was no significant difference at 12h (p<0.050). The incidence of nausea and vomiting was not significantly different between the two groups (Table 4).

Paracetamol and methadone consumption were significantly lower in the DEX group as compared to the control group at 3, 6 and 12h after surgery (p<0.05) indicating that the use of DEX reduced the consumption of analgesics.

Table 1. Demographic characteristics of the participants in the two groups

Characteristics	Group		Statistical analysis*	P-value
	Dexmedetomidine	Control		
Gender, N (%)	18 (72%)	17 (68%)	0.740	0.712
Male	7 (28%)	8 (32%)		
Female				
Age (years) (mean ± SD)	40.68 ± 10.64	42.36 ± 11.75	3.107	0.501
Weight (kg) (mean ± SD)	81.28 ± 14.61	73.32 ± 14.48	0.250	0.109
ASA (I: II)	25:0	25:0	3.203	0.205

SD: Standard Deviation, ASA: American Society of Anesthesiology
*Chi-square

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Table 2. Comparison of visual analogue scale score of the two groups at rest

VAS score	DEX group	Control group	df1	df2	Statistical analysis	P- value
1h	1.24±0.92	1.92±0.75	1	48	0.351*	0.004
3h	1.24±0.92	3.84±2.07	1	48	0.451*	0.010
6h	1.72±1.42	3.84±1.65	1	48	0.184**	0.010
12h	1.28±1.27	2.92±1.86	1	48	0.010**	0.001
24h	0.56±0.58	1.04±0.61	1	48	0.101**	0.008

VAS: visual analogue scale

*Independent t-test; **Mann–Whitney U test

Table 3. Mixed analysis of variance on the variables of VAS, group and time

Variables		Sum of Squares	df	Mean Square	F	Sig.	Effect
VAS	Greenhouse-Geisser	119.124	2	44.290	19.658	0.000	0.291
	Huynh-Feldt	119.124	2	40.74	19.658	0.000	0.291
	Lower-bound	119.124	1	119.124	19.658	0.000	0.291
VAS× Group	Greenhouse-Geisser	38.340	2	14.255	6.327	0.001	0.116
	Huynh-Feldt	38.340	2	13.113	6.327	0.001	0.116
	Lower-bound	38.340	1	38.340	6.327	0.015	0.116
Error (VAS)	Greenhouse-Geisser	290.876	129	2.253	--	--	--
	Huynh-Feldt	290.876	140	2.073	--	--	--
	Lower-bound	290.876	48	6.060	--	--	--

Table 4. Comparison of Clinical symptoms between the two groups

Variable		DEX group	Control group	df1	df2	Statistical analysis	P- value
Arterial blood pressure (mean ± SD)	Baseline	91.38±10.65	91.25±7.67	1	48	0.209*	0.932
	1h	88.96±10.49	89.28±7.34	1	48	0.004*	0.999
	3h	88.14±10.60	88.82±7.10	1	48	0.24*	0.751
	6h	87.53±9.75	87.78±6.44	1	48	0.900	0.962
	12h	88.13±10.61	88.45±7.61	1	48	0.781*	0.957
	24h	86.05±6.36	87.53±9.40	1	48	0.928*	0.531
Heart rate (mean ± SD)	Baseline	71.36±7.70	74.36±11.95	1	48	0.057*	0.201
	1h	70.20±7.74	71.08±9.24	1	48	0.151*	0.730
	3h	70.16±8.46	74.08±10.59	1	48	0.095	0.121
	6h	71.32±7.94	73.96±9.58	1	48	0.113*	0.210
	12h	70.04±7.54	73.56±9.48	1	48	0.095*	0.110
	24h	70.20±7.74	71.08±9.24	1	48	0.023*	0.787
Shivering N (%)	3h	0 (0%)	5 (20%)	--	--	0.53**	0.020
	12h	0 (0%)	1 (4%)	--	--	0.15**	0.521
Nausea and vomiting N (%)	1h	0 (0%)	1 (4%)	--	--	0.57**	0.510
	3h	0 (0%)	2 (8%)	--	--	0.98**	0.232
	6h	0 (0%)	1 (4%)	--	--	1.30**	0.501
	12h	0 (0%)	0 (0%)	--	--	-	-
	24h	0 (0%)	0 (0%)	--	--	-	-

* independent t-test; ** Chi-square

Discussion

To the best of our knowledge, this is the first randomized clinical trial (RCT) which investigated the effect of local dexmedetomidine injection as the sole local anesthetic agent as an adjuvant to general anesthesia in patients undergoing perianal surgery. Perianal surgery is associated with a considerable amount of pain; therefore, appropriate pain management is crucial (17). Although general or regional anesthesia is usually used for anorectal surgery, the use of local anesthesia for anorectal surgery has recently gained an increasing amount of interest (9).

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The results of the present study indicated that the local injection of dexmedetomidine reduced postoperative pain and the need for analgesics in patients undergoing perianal surgery. Dexmedetomidine is a selective alpha-2-adrenoreceptor agonist with analgesic, sympatholytic, and opioid-sparing properties. It is widely used for sedation during surgical procedures. However, the use of dexmedetomidine as an analgesic agent remains debating, and it is typically administered as an adjunct to other analgesics (18). Similar to the findings of the current research, previous studies have shown that the addition of dexmedetomidine to wound infiltration of ropivacaine and bupivacaine is effective to reduce postoperative pain scores and analgesic requirement (15, 19-21). A randomized clinical trial of 61 patients undergoing hemorrhoidectomy showed that injection of ropivacaine is effective to reduce postoperative pain and fentanyl consumption. Moreover, their results suggested that adding dexmedetomidine to ropivacaine increases the analgesic properties of local ropivacaine (20). Moreover, Cheung et al. in a double-blinded RCT evaluated 33 patients undergoing bilateral third molar surgery under general anesthesia and demonstrated that local administration of dexmedetomidine (1μg /kg) to the surgical wounds at the end of the surgery reduced pain scores in 1 to 72 hours after surgery (22). The results from another study on 60 women undergoing abdominal hysterectomy indicated that adding dexmedetomidine to bupivacaine in wound infiltration reduces postoperative pain scores and analgesic consumption as compared to bupivacaine alone (23). The administration of dexmedetomidine via the neuraxial route has been found to be effective on both somatic and visceral pain, it also reduces postoperative pain and extends the duration of analgesia, although it may carry a risk of causing bradycardia (24). The results of the present study indicated that dexmedetomidine reduced postoperative pain and the need for analgesics in patients at 1, 3, 6, 12, and 24 hours after the surgery. A variety of dexmedetomidine doses, in combination with several analgesic medications, have been explored in numerous studies. However, the precise dosage of dexmedetomidine to be used as an adjunctive medication alongside other intravenous drugs during the perioperative period remains a topic of debate (25).

In the current research, the local injection of dexmedetomidine did not significantly affect the participants' heart rates and mean blood pressure. This is in contrast to the findings of Cheung et al., which suggested that the local administration of dexmedetomidine reduces heart rate and systolic blood pressure in the immediate postoperative period following molar surgery (22). On the other hand, a meta-analysis of nine studies that compared dexmedetomidine and fentanyl as adjuvants to local anesthetics in spinal anesthesia found no significant difference in the incidence of hypotension and bradycardia (26).

The incidence of nausea and vomiting and shivering in the present study did not differ between the participants receiving local dexmedetomidine and the controls. In general, dexmedetomidine has been suggested to have anti-nauseating and anti-shivering effects (27, 28). However, most of these studies have administered dexmedetomidine intravenously, whereas in the current study dexmedetomidine was applied locally. In support of the findings of the present study, a meta-analysis comparing dexmedetomidine and fentanyl as adjuvants to local anesthetics did not find a significant difference in the occurrence of side effects such as nausea, vomiting, shivering and respiratory depression (26).

Dexmedetomidine has been effectively utilized in pediatric patients as an adjunct in caudal epidural procedures. The use of 1–2 mcg/kg dexmedetomidine in conjunction with bupivacaine extends the duration of analgesia without significant side effects (29). However, whether dexmedetomidine is superior to clonidine in this context remains unclear (30). Various doses of bupivacaine have been used across different studies (31). However, it has been observed that the addition of 2 mcg/kg of dexmedetomidine to 1 ml/kg of 0.25% caudal bupivacaine significantly enhances analgesia following anesthetic recovery in children aged between 6 months and 6 years. Importantly, this combination does not appear to increase the incidence of side effects (32). Dexmedetomidine is increasingly being utilized across various areas of anesthesia practice. Apart from a few reports of animal studies, no significant side effects have been reported. Similarly, this study did not report any side effects associated with this drug. Therefore, dexmedetomidine is likely to remain a staple in the anesthetist's toolkit.

The present study had some limitations. Firstly, the small sample size and the single-center approach might have limited the generalizability of the results. Secondly, the control group did not receive a placebo, which could have helped to eliminate the placebo effect. Lastly, we did not compare the effects of local versus IV administration of dexmedetomidine.

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Implications for practice

The results of the current research showed that the local administration of dexmedetomidine reduces pain scores and analgesic consumption in patients undergoing general anesthesia for perianal surgery. However, no significant difference was found between dexmedetomidine group and placebo group in terms of hemodynamics status, nausea and vomiting, and shivering. In clinical research on dexmedetomidine, outcomes, pain management, and premedication are the primary areas of focus. Dexmedetomidine can be suggested as an analgesic with minimal side effects for patients after perianal surgery. However, it is suggested that the impact of dexmedetomidine sedation on the outcomes of critically ill patients, its analgesic effect, and its organ-protective properties be focused in future research.

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Conflicts of interest

The authors declared no conflict of interest.

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Authors' Contributions

Mohammad Alipour: designing the reaserch, , Seyed Farshid Reza Mirsayah: data collection, Kiarash Roustai Geraylow: data collection, Abbas Abdollahi: writing the original draft, Benyamin Fazli: data interpretation and analysis, Mahsa Abazari Torghabeh: writing the article. All authors have read and agreed to the published version of the manuscript.

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