Posterior Cervical Discectomy via Keyhole Foraminotomy: A Case Series Comparing Microdiscectomy with Endoscope-Assisted Discectomy

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ABSTRACT

AIM: Anterior cervical discectomy and fusion (ACDF) has become the standard surgical treatment of cervical disc hernias (CDH), however, its complications including dysphagia, recurrent laryngeal nerve injury, pseudoarthrosis, implants and graft problems, adjacent segment disease have been well-known. Posterior cervical discectomy (PCD) via posterior keyhole lamino-foraminotomy may be a solution to avoid from these complications. To report the clinical outcomes of microdiscectomy (MD) and endoscope assisted discectomy (EAD) techniques via the posterior approach in patients with cervical disc herniations (CDHs).

MATERIAL and METHODS: The data were obtained from retrospective review of the patient’s charts and the latest follow-up examination.

RESULTS: A total of 83 cases with CDH who were treated by posterior cervical discectomy (PCD), between 2010 and 2019, were reviewed. MD was used in 42 patients (male: 20, female: 22) with a mean age of 51.1 years. In MD group, all patients had pain, and 26 of them had additional weakness. Visual analogue scale (VAS) neck score was 7.72, VAS arm score was 8.83; PROLO score was 7.41. EAD was used in 41 patients (male: 26, female: 15) with a mean age of 38.7 years. In EAD group, all patients had pain, and 20 of them had additional weakness. VAS neck and arm scores were 7.75, and 8.72, respectively; PROLO score was 7.44. Mean follow-up time was 24.7 months. The scores at the latest exam are as follows: in MD group, VAS score for neck was 2.32, for arm 1.11; PROLO score was 9.58; in EAD group, VAS score for neck was 2.18 and for arm 0.97; PROLO score was 9.66. Both surgical techniques were success with statically significance (p≤0.05) according to the scores. The techniques were equally effective while postoperative VAS (p>0.412) and PROLO (p>0.980) scores were similar in both groups.

CONCLUSION: Both approaches are effective for selected patients with soft cervical disc herniation in which settled lateral location. Both techniques allow working with two handle, therefore facilitating the gentle manipulation that can obtain for avoiding hazardous effect to spinal cord and nerve root.

KEYWORDS: Cervical disc herniation, Key-hole foraminotomy, Endoscopy, Microdiscectomy, Posterior approach

INTRODUCTION

Anterior cervical disectomy and fusion (ACDF) has become the standard surgical treatment of cervical disc hernias (38). Its complications include dysphagia, recurrent laryngeal nerve injury, and perforation of the esophagus (4,27,37,48). Pseudoarthrosis is the most common problem encountered during the follow-up period that could be addressed using implants and graft problems may require graft revision (29,32,44). Nevertheless, bone fusion was achieved despite the fact that adjacent segment disease may occur as the next trouble (8). Spine surgeons are working on means to prevent ACDF-related complications and posterior cervical disectomy (PCD) via posterior keyhole laminoforaminotomy is one of these milestone procedures (8,10,26). However, PCD requires muscle dissection reason why its use is not widespread. Recently, the introduction of the surgical microscope and speculum- or tube-like retractors minimizing muscular dissection has facilitated the posterior approach (7,12). Besides, PCD has been shown to shorten hospital stay, lessen tissue injury, and lower the amount of blood loss due to ACDF (14,47). Moreover, some reports reveal that PCD is an effective technique for preserving motion at the operation site (since it does not require fusion) and allows for early recovery, thus lowering the risk of adjacent segmental disease (24,28). Therefore, we retrospectively reviewed the postoperative clinical outcomes of PCD performed with posterior cervical microdiscectomy (PC-MD) or posterior cervical endoscope-assisted discectomy (PC-EAD) techniques.

MATERIAL and METHODS

Patients

From August 2010 to November 2019, 351 patients who suffered from cervical disc hernia (CDH) were treated at our hospital. PCD was performed in 104 patients of whom 83 were followed up. We reviewed the records of the latest control examinations of 42 (75%) patients who had PC-MD and 41 (85%) patients who had PC-EAD. We excluded patients whose follow-up period was shorter than 12 months.

A lateral cervical plain radiograph, a computed tomography (CT) scan, and a magnetic resonance imaging (MRI) scan were used to diagnose CDH, assess cervical spinal alignment, and to demonstrate degenerative changes (loss of height, black disc, calcification, osteophyte formation) in all patients. All patients underwent PC-MD or PC-EAD technique via a posterior approach to treat single-level, soft cervical disc herniation. Patients were included if they had signs of radiculopathy compatible with signs on a preoperative cervical MRI (Figure 1A-C), a laterally-located single-level soft disc hernia on radiological imaging, and those with persistent signs after conservative treatment for minimum four weeks, or whose symptoms worsened over this period.

All patients were operated upon by the same surgeon (AD). The PC-MD technique was preferred in patients with soft disc accompanied by signs of degeneration (osteophytes) at a foraminal level on a preoperative plain film and/or CT scan, reduced disc height, and facet joint hypertrophy. PC-EAD was performed in patients without any sign of degeneration.

Figure 1: MRI scans revealed a soft disc herniation that settled at the left foramina of C6–7 (A), CT images showed degenerative findings such as reduced disc height, osteophytes at the different levels, but herniation was not calcified and no stenosis at the foramen (B), removed disc and effective decompression was seen postoperative MRI scans (C).
We excluded patients with segmental instability, CDH with midline location, posterior longitudinal ligament (PLL) calcification, central cervical stenosis and/or foraminal stenosis without CDH, multilevel CDH, or suspected infection or tumor in the cervical vertebrae. Patients who were followed up for less than 12 months were also excluded.

**Surgical Technique**

**PC-MD:** The patient was placed on the operating table in the prone position with their neck slightly flexed under general anesthesia. The disc level was determined using fluoroscopy. A skin incision of approximately 1.5 cm long was made in a linear fashion approximately 2 cm away from the midline to center of the disc space/foramina. After the skin and fascia were opened, muscle layers were explored with the help of special speculum-like retractors. After confirming a disc space, the upper part of the lower lamina was drilled first beginning from the upper part of the lower lamina using a high-speed drill under the operating microscope. Thus, a keyhole shaped foraminotomy was carried out, 1/3 in the upper lamina and 2/3 in the lower lamina (Figure 1A). The ligamentum flavum was excised en masse with the epidural venous plexus by coagulating the former with a bipolar cautery in order to minimize bleeding from the epidural venous plexus. Moreover, the dural sac and the nerve root were exposed, and the root was gently retracted from its axillary part to reach the extruded disc and to remove the sequestered disc fragment. After confirming that the nerve root and neural structures were relieved at the disc space, hemostasis was achieved, marking the end of the surgical procedure (Video 1).

**PC-EAD:** The surgical procedure was begun after the patient had been prepared as in the PC-MD technique. We used Easy-GO® system (Karl-Storz, Tuttingen, Germany) for PC-EAD procedure. Following skin incision, the layers were explored by dilating them with the help of tube-shaped dilators. After confirming the target disc level under fluoroscopy, the procedure was continued under endoscopic view with a 15-mm diameter working canula. In the PC-EAD technique, bone removal from the upper lamina was not needed, thanks to the change of direction of the working cannula and its angled vision. Thus, the upper 2/3 of the lower lamina was first drilled, followed by the upper lamina as deemed necessary by a visual assessment of the surgeon (Figure 1B). The ligamentum flavum was coagulated within lifting by bipolar cautery. The maneuver involved the coagulation of venous plexus beneath the flavum and its removal en masse with the epidural venous plexus without bleeding. If they were separately removed, extensive bleeding could have occurred. The dural sac and the nerve roots were exposed, and the root was gently retracted from its axillary part to reach the extruded disc and to remove the sequestered disc fragment. After confirming that the nerve root and neural structures were relieved at the disc space, hemostasis was achieved, marking the end of the surgical procedure (Video 2).

Patients in both groups were mobilized approximately 8 hours after surgery and were discharged on the first postoperative day. They were prescribed the wearing of neck collars for only three days after their discharge.

**Follow-up**

The patients underwent routine clinical follow-up at 3, 6, and 12 months after surgery, and a radiological control was performed at 12 months. Cervical lordotic alignment and adjacent segment degeneration were checked at the radiological follow-up using a radiograph and an MRI at 12 months. Their final control was done via outpatient clinic examination or phone call. A 10-point visual pain scale score was used to rate neck and arm pain, and the PROLO score to assess the final status (Table I) (39).

**Statistical Analysis**

The Statistical Package for Social Sciences (SPSS® for Windows) software was used to compare the preoperative and postoperative parameters among the two groups. The data set was tested for normality using the Kolmogorov-Smirnov test. Non-parametric tests were used for skewed data. The Wilcoxon test was used to compare preoperative and postoperative values. The Mann Whitney-U test was used to compare the two techniques to parameters such as duration of operation, volume of bleeding, and postoperative values. A p-value of less than 0.05 was considered statistically significant.

**RESULTS**

Table II displays the demographic features of patients. Table III summarizes patient characteristics, surgical findings, and postoperative course.

The mean operative time was 74.39 (50–80) min for PC-MD and 81.4 (55–90) min for PC-EAD. Both groups had similar postoperative durations of hospital stay. Volume of bleeding...
Postoperative VAS and PROLO scores showed significant improvement over preoperative values, but outcomes were similar at both groups. VAS score for neck pain in PC-MD group was slightly more than in PC-EAD cases, though not significantly different between them (Table IV). Total PROLO score was 9 and 10 points in 75 (90.4%) patients, and rate of the best success group was 90.3%, but 3 cases (3.6%) experienced moderate and/or poor scores. No severe permanent postoperative neurological complications occurred. CSF leak developed in three patients in the PC-MD group and three patients in the PC-EAD group; this complication was managed by administering fibrin glue into the operative field perioperatively. They were later discharged without any neurological sign or wound site complication, and they suffered no complications at follow-up. One patient from each group had persistent postoperative pain, and a control MRI examination showed complete disc removal and full decompression of the nerve root. Such patients received physical therapy followed by gabapentin, which improved their symptoms. One patient in the PC-EAD group had recurrence of pain five months after surgery. An MRI scan revealed a recurrent CDH that was treated by ACDF.

Among patients who were initially treated with PC-EAD, three switched to PC-MD and were analyzed in the PC-MD group. In two of them, the change was made due to an inadequate view of the surgical field owing to an epidural venous bleeding. The other patient was switched to PC-MD because of the entry of a dilator into the spinal canal through the interlaminar space while placing the dilator tubes. That patient developed left-sided postoperative hemiparesis, but regained...
his preoperative motor strength after being treated with postoperative physiotherapy. Although numbness persisted thereafter, he returned to his previous work after treatment with pregabalin.

**DISCUSSION**

PCD via posterior keyhole foraminotomy could be performed with microscopic or endoscopic systems and is effective in about 93.6% of patients (6,11,19,35). Current surgical tools minimize muscle injury, ensure a lower rate and severity of postoperative pain, and shorten the time of discharge and full recovery. Fusion is unnecessary, so implant complications and pseudarthrosis risk are both eliminated, and permits a natural-like aging process of spine with less risk of adjacent segmental disease (1,10).

**Anterior Versus Posterior Approaches**

ACDF is associated with several complications including neurological deterioration, dysphagia, esophageal perforation, hoarseness, vascular injury, Horner syndrome and postoperative hematoma (44). Vascular injuries may involve embolic stroke episodes originating from ruptured atheroma plaques due to excessive manipulation of the carotid arteries (16). Esophageal perforation is rare (0.25%) but is associated with high mortality and morbidity due to mediastinitis, abscess, and tracheo-esophageal fistula formation (17). The leading long-term complications of anterior cervical discectomy are related to implants and they include collapse, displacement or failure of fusion (29,32). Dislocation of a cage or bone graft has an incidence of 8%, failure of fusion in 5% for single-level, and 15% for multilevel discectomies (27,29,32,37,44). At 10-year follow-up, 25% of patients were admitted to the hospital with adjacent segmental disease, of whom 2.9% each year required reoperation (18). Moreover, Goffin et al. reported that radiological adjacent segmental disease with or without symptoms developed in 92% of patients after 5 years (15). Biomechanical alterations are likely to be responsible for adjacent segmental disease and motion-sparing treatment modalities have been proposed for prevention (8,41). Although biomechanical studies have shown that the use of disc prostheses preserves motion (46), heterotopic ossification (9.4%–17.8%) and spontaneous fusion (2.9%–11%) during follow-up (23,26). ACDF is a particularly risky technique for certain professions such as vocalists, soldiers and athletes (19).

Anterior and posterior approaches can achieve similar success rates with microdiscectomy and endoscopic approaches (6,11,19,35). In a study comparing anterior and posterior endoscopic surgeries, no significant difference was observed between the two groups, although posterior endoscopic surgery was more effective for treatment of sequestered discs (47). No significant difference was reported between ACDF and keyhole foraminotomy in terms of clinical effectiveness and complications (14). A meta-analysis revealed that both techniques had similar clinical effectiveness, while complications were relatively more common in the ACDF group (ACDF - 7% / PCD 4%) and reoperation rates were more common in the PCD group (ACDF - 4% / PCD 6%), although these differences were not significant. Moreover, patients in the PCD group experienced more adjacent segmental disease and less implant procedure, which was an overall advantage (24).

**Case Selection for PCD**

Laterally sequestered/migrated discs are more suitable for PCD, particularly its endoscopic variety (2). Wen et al. reported that an extruded/sequestered mass at an average distance of 5.41 (1.40) mm from the dural sac was safe and ensured successful outcomes (43). Medially located CDH must be operated via anterior approach, though posterior techniques are indicated for selected cases (14).

The sequester is easily removed if it migrated inferiorly through axilla. Superiorly migrated disc could also be removed by the
nerve-hook maneuver; however, surgeon should extend to upper part of keyhole and check the shoulder of the nerve root if it descended to more than half of the vertebral body (or is not certain if it could be removed completely).

The consistency of a herniated disc is also important as it is not easy to remove calcified hard discs accompanied by osteophytes via the posterior approach. Moreover, the disc level is completely covered by nerve root due to cranial trajectory of the unco-vertebral joint. Placing a surgical tool in a disc space with such a direction would require significant retraction of the nerve root, thereby leading to compression and injury of the latter (Figure 3). Hence, discs with soft formation that can be removed without vigorous manipulation are suitable to undergo PCD. The procedure performed in this approach entails the removal of a sequestered/migrated part (sequestrectomy). Since compression is anteriorly directed in hard discs accompanied by osteophytes, the posterior approach is an indirect decompression. On the other hand, the height of the intervertebral foramen is also reduced as a result of collapsing disc space during the degenerative process. In our opinion, removal of osteophytes by anterior discectomy allows for direct decompression of cervical disc hernias accompanied by osteophytes while the disc space is elevated by placing an interbody cage, which further enlarges the foramen.

In our clinic, ACDF was preferred for CDH cases with degenerative changes (osteophytes, foraminal stenosis, and multilevel cervical discectomies). PCD is not performed for calcified/hard discs. Similarly, Kim et al. performed an endoscopy-assisted technique for foraminal soft discs and excluded patients with spinal cord compression, and facet joint degeneration or a calcified disc (20). Reutten et al. considered the presence of a foraminal or lateral disc as an indication for surgery among 87 patients operated with PCD via full endoscopic approach; they excluded patients with instability and deformity, a medially located disc, or PLL calcification (33). At a follow-up duration of 24 months, they reported 96.6% clinical success. However, our series had a clinical success rate of 90.3% at a 24.7 months follow-up.

**Biomechanics**

PCD is a motion-sparing technique that employs minimally-invasive approaches (1,10). Studies on degenerative processes and vertebral alignment after PCD evaluated disc heights and sagittal alignments through control images taken during follow-up visits. No significant reduction in disc height or progression to kyphosis at the sagittal alignment was observed, and segmental motion was maintained. The authors also admitted the shortness of the follow-up time, emphasizing the need for studies with longer follow-up time to be undertaken (20,21).

A biomechanical comparison of anterior cervical discectomy and keyhole foraminotomy suggests that neither of them causes overt instability; in anterior discectomy, however, an approximately two-fold increase occurs in segmented motion and a need for stabilization may arise later (9). Yuchi et al., in a biomechanical study based on the finite element method, reported that segmental motion significantly increased after anterior endoscopic foraminotomy compared with both the control and posterior keyhole foraminotomy groups. Although a slight increase occurred in the posterior keyhole foraminotomy group compared to the control group, it was not significant (49). Generally, anterior approaches cause enhanced FSU motion, which requires fusion. Hence, anterior approaches inevitably progress to ACDF. It has been reported that keyhole foraminotomy and anterior approaches provide similar degrees of foraminal dilation, and no increase occurs in segmental range of motion among patients undergoing keyhole foraminotomy (28). Similarly, an analysis of our patients’ preoperative and postoperative MRI findings at a mean follow-up time of 24.7 months did not reveal any degenerative change on the existing findings at the adjacent disc spaces.

Adjacent segmental degeneration is a long-term complication of ACDF, whereas PCD procures preservation of motion as fusion and implants are not used. Alvin et al. reported that ACDF and the posterior keyhole approach were similar in terms of clinical efficacy but ACDF was economically burdensome (3). Another study revealed an increased cost associated with the use of implants (25).

![Figure 3: Illustrative drawings showed that relationship nerve root, disc, and disc space is sensitive and rigor, because uncovertebral joint turned to upwards at the foramen and covered by nerve root; A) demonstrated the enveloping of them via oblique and laterally perspectives, B) illustrated a herniated disc through posterior approach and the extruded fragment must be removed by a nerve hook via pulling it from the underneath without impolite manipulation.](image-url)
Complications
A learning curve is an inevitable aspect in endoscopic approaches (2,5,40). We experienced a case of dural injury when a dilator tube entered into the canal through the interlaminar space while placing dilator tubes. We then switched to microdiscectomy in order to get a clearer view of the nerve root and spinal cord, and to check the need for repair. That patient suffered a temporary postoperative hemiparesis and persistent sensory complaints; he was able to return to work following gabapentin treatment. In two patients, the operation initially began with PC-EAD and switched later to PC-MD because of a poor view of the surgical field owing to venous bleeding. The distinction between the epidural venous plexus and ligamentum flavum is usually difficult, and venous bleeding is often encountered during flavectomy in cervical surgery. Positioning a patient in the prone position obstructs venous return and complicates stoppage of such bleeding. Therefore, the flavum was coagulated with bipolar cautery and removed in both PC-MD and PC-EAD approaches. However, a switch was made to the PC-MD technique in two of our patients at the beginning of our series.

Another complication seen in our series was a CSF leak. CSF leaks typically occur as a result of dural injury at an axilla of a nerve root. PCD allows the removal of the disc from the injured nerve root. In the axilla, dural repair with primary suturing is challenging due to its direction and anatomical location. The risk of injury to nerve fibers passing by that location during suturing could be a possible threat. Some authors have reported that the dura can be repaired with tools such as the u-clip used in abdominal laparoscopic procedures (30). However, it is troublesome to seal the injury usually developing in the antero-inferior direction at the axillary part of a nerve root with a favorable angle. Likewise, patches of muscular and/or fatty tissue are utilized for dural injury repair. It appears worrisome that a graft placed at an axilla of a nerve root causes irritation of the relatively narrow cervical intervertebral root by creating a mass effect. Six patients in our series suffered dural injury; three (7.1%) patients in the PC-MD group and 3 (7.3%) patients in the PC-EAD group developed intraoperative CSF leak that was managed by spraying a fibrin glue into the operative field. Those patients were discharged free of any neurological sign or wound problem and remained well throughout follow-up.

Although recurrent herniation is the major criticism against PCD approaches, several authors reveal that they are not significantly different from ACDF (42). Selvanathan et al., in a comparative study between ACDF and posterior keyhole foraminotomy, two patients from the ACDF group underwent reoperation due to adjacent segmental disease and one patient due to the need for foraminal decompression (2% in all), while 1 (2%) patient from the keyhole foraminotomy group required surgical intervention due to recurrence of symptoms at a 2-year follow-up visit (36). Wu et al., reported a meta-analysis that included 24 studies with posterior endoscopic procedures. They noted a reoperation rate of 4.8%-5.3% (45). Cervical spinal alignment was analyzed for recurrence in patients who were re-operated on posterior discectomy.

Although Kim et al. reported that cervical curvature does not worsen after PCD (21), Zeng et al. presented a case series that included three patients with recurrence or development of progressive kyphosis who later underwent ACDF (50). Initial marked degeneration, bony spur and/or osteophytes were associated with other levels, while cervical kyphosis could cause inadequate decompression and required reoperation (31). The authors suggested ACDF procedure in patients with recurrence after posterior discectomy (31,50). Only one (1.2%) patient in our series was diagnosed of recurrent herniation and was re-operated through ACDF.

Comparison of Posterior Approaches
Marked differences exist between anterior and posterior approaches with respect to patient selection and technical aspects. However, different posterior approaches are fundamentally similar. Thus, their success rates are similar to one another as well; in a meta-analysis, the clinical success rates of posterior approaches was 93.6% for patients who underwent PC-MD and 89.9% PC-EAD, and both techniques were statistically similar. In addition, both techniques appeared similar in terms of complication rates and the need for reoperation (45).

Fessler and Khoo compared 25 endoscopic cases and 25 microscopic keyhole foraminotomy cases; they reported complete recovery rates of 92% and 87% for radiculopathy and neck pain, respectively, in the endoscopic group, and 88% and 89%, respectively, in the microscopic group. Both techniques were similar (13). Kim and Kim randomized 19 patients to the microscopic group and 22 to the endoscope-assisted keyhole foraminotomy group. Though a marked reduction in the length of hospital stay, postoperative analgesic use, and intraoperative bleeding volume were observed, the clinical outcomes were similar in both groups (22). The same study also reported that endoscope-assisted PCD had a complication rate of 0%-4.3% while the corresponding figure for full endoscopic technique was 3%-5%, with both figures being similar (22). PC-MD and PC-EAD have similar success rates via posterior approaches according to the PROLO and VAS scores; however, the VAS for neck pain in the PC-MD group was slightly more than in the PC-EAD group. We hypothesize that this difference was related to the dilatation of muscle through incrition of speculum-like retractor.

Cervical sequestrectomy in posterior approaches is usually performed from the axilla of a nerve root. The ability to perform keyhole foraminotomy with both PC-MD and PC-EAD offers a surgeon the advantage of using both hands. Keyhole foraminotomy does not only provide a corridor for sequestrectomy, but also for an adequate decompression at the foramina. By this way, the nerve root can be retracted gently, and the disc can be removed by a simple draw-side maneuver using micro tools. It is clear that such fine manipulations would be safer than those carried out using working cannula in pure endoscopic systems. Likewise, disc removal is achieved by retracting the nerve root with invasively-working cannula during posterior full endoscopic cervical discectomy. Therefore, numbness is more common after surgical procedures performed with full endoscopic
systems (45); we believe that the aforementioned temporary sensory complaints were related to that retraction maneuver.

Reutten et al. reported that full endoscopic approaches in posterior cervical techniques do not directly aim at the disc as in lumbar pathologies, although laminoforaminotomy is performed to a lesser degree. He stated that the aim of posterior approaches is to avoid surgical trauma under a good view of the surgical field, and added that full endoscopic procedures fall short in the posterior cervical region. He drew attention to the term “full endoscopic” for techniques applied transdiscally, without necessitating bone resection as is the case for lumbar and anterior cervical approaches (33,34). Yet, cervical disc hernias are underneath the nerve root and must be removed from the axillary direction. Thus, keyhole foraminotomy offers an important advantage for safe disc removal via PS-MD and PS-EAD. We therefore postulate that the similar clinical success rates encountered in both techniques could be linked to the fact that keyhole foraminotomy was feasible in both of them.

Limitations

The first limitation of our study includes the use of a single institution and surgeon specialized in microneurosurgery and endoscopic procedures. This could lead to bias for case selection. Secondly, the study was a nonrandomized retrospective one. Finally, the follow-up period was short. Thus, we recommend further studies with prospective, multicentric, and randomized designs with long-term follow-up.

CONCLUSION

A sequestered/migrated disc can be removed using a minimally-invasive technique via keyhole foraminotomy using either PC-MD or PC-EAD approaches with favorable outcomes in selected cases. Minimally-invasive posterior approaches provided keyhole foraminotomy; thus, a surgeon skillful with both hands also enhanced this surgical window. These approaches avert the natural aging process by least affecting muscle tissue, avoiding bone fusion, and/or implants.

AUTHORSHIP CONTRIBUTION

Study conception and design: AD, RK
Data collection: RK, DKG, EI, GG
Analysis and interpretation of results: AD, RK, DKG, ADB
Draft manuscript preparation: AD, RK; DKG, ADB
Critical revision of the article: AD, RK
Other (study supervision, fundings, materials, etc...): AD, RK, DKG

All authors (AD, RK, DKG, EI, GG, ADB) reviewed the results and approved the final version of the manuscript.

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