Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2022**; 49(2): 050
http://doi.org/10.31083/j.ceog4902050

Original Research

The effect of intraoperative antiemetics on postoperative nausea and vomiting in patients receiving intrathecal morphine for elective caesarean deliveries

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Academic Editor: Michael H. Dahan
Submitted: 10 May 2021 Revised: 12 August 2021 Accepted: 20 August 2021 Published: 14 February 2022

Abstract

Background: The incidence of postoperative nausea and vomiting (PONV) when intrathecal morphine (ITM) is used for caesarean delivery (CD) is up to 80% without antiemetic prophylaxis. Prophylactic antiemetics can reduce this rate by 50%, except for dexamethasone that did not show to be effective in this context. Combinations showed divergent results. We investigated the incidence of PONV when different combinations of antiemetics were used for CD in parturients receiving ITM. **Methods**: Retrospective, single centre cohort study of patients undergoing elective CD with ITM between January 2016 and October 2017. The primary outcome was the incidence of PONV requiring treatment in the first 24 hours following CD. Interactions were sought using multivariate modelling for predictors of PONV following surgery. **Results**: Overall, 598 women were included in the study. The rate of PONV requiring treatment was 29.1%. The rate of PONV decreased with increasing numbers of prophylactic medications ($p < 0.001$). Women who did not experience PONV received a greater number of antiemetics in the operating room ($p < 0.001$). There was a dose response relationship between ITM dose and PONV rate ($p < 0.001$). Dexamethasone, either alone or in combination with other agents was not protective against PONV when compared with other drug combinations ($p = 0.08$). **Conclusions**: We have demonstrated an inverse relationship between the number of prophylactic antiemetics given and the rates of PONV after caesarean delivery in the context of intrathecal morphine use. Dexamethasone use, either alone or in conjunction with other drugs did not offer advantages over other combinations where dexamethasone was avoided.

Keywords: Antiemetic prophylaxis; Caesarean delivery; Caesarean section; Intrathecal morphine; Postoperative nausea and vomiting

1. Introduction

Post-operative nausea and vomiting (PONV) is a common complication following elective and emergent caesarean deliveries (CD). The main reason for this complication is the use of intrathecal morphine (ITM) to treat post-operative pain [1]. Studies have shown PONV rates of up to 60% when this medication is given without antiemetic prophylaxis [2]. The routine use of antiemetic prophylaxis can reduce this rate by 50% [2,3].

Numerous classes of medication have been studied to minimize PONV following elective CD. Serotonin, dopamine, cholinergic and histamine receptor antagonists and corticosteroids such as dexamethasone are commonly used agents. Previous studies demonstrated that all of these drugs except dexamethasone were effective in preventing PONV post CD [3]. This medication did not show benefits when used as a solo medication and showed only marginal gains when combined with droperidol [2–6].

The purpose of this study was to determine the impact of different combinations of antiemetics given in the intra-operative period on the rate of PONV in parturients undergoing elective CD in the context of ITM. We hypothesized that there would be an inverse correlation between the number of antiemetics utilized and the incidence of PONV. A secondary hypothesis was that dexamethasone, either alone or in combination, would not be efficacious in the prevention of PONV.

2. Methods

This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [7]. The Fiona Stanley Hospital (FSH) is a tertiary obstetric centre serving the South Metropolitan area of Perth in Western Australia, where approximately 3300 births take place per year. Since opening in October of 2014, the hospital has rapidly increased the capacity of its maternity and neonatal units providing tertiary obstetric care to approximately 1 million patients or 35% of the total population of the city.

We conducted a retrospective analysis of women who underwent elective CD where ITM was used as a part of a post-operative multimodal analgesic regimen between the

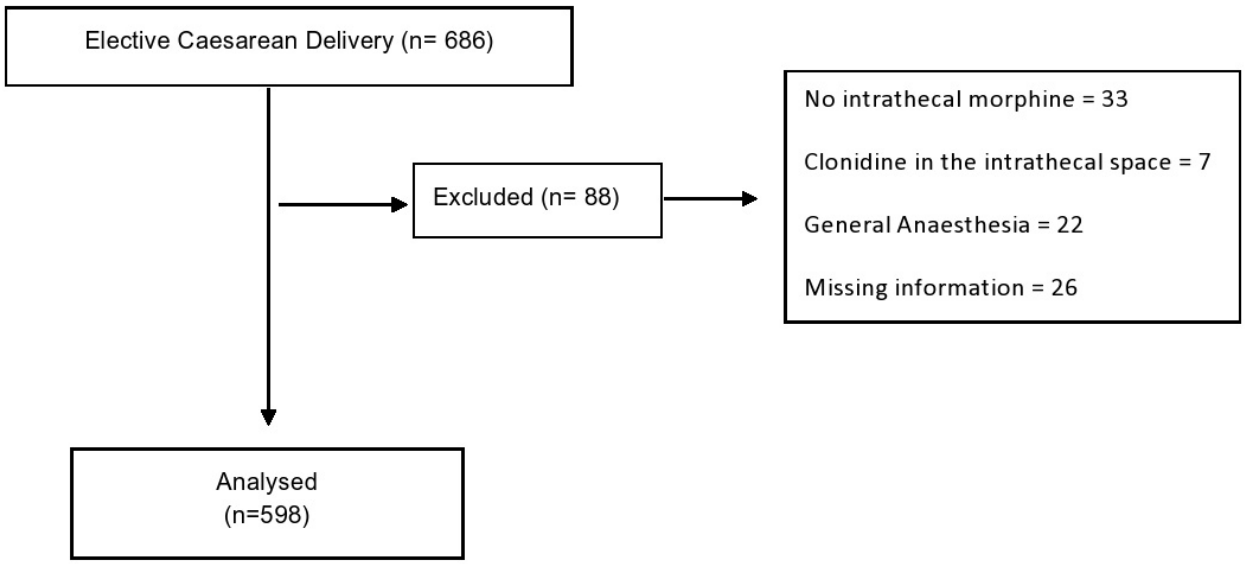

Fig. 1. Retrospective cohort study flowchart.

1st January 2016 and the 31st October 2017. Patients were excluded if additional additives, e.g., clonidine were added to the intrathecal space; when regional anaesthesia failed; when the ITM dose was less than 100 mcg or greater than 150 mcg or if sufficient information could not be obtained from the paper and electronic perioperative records.

Patients were identified through their unique medical record number (MRN) in the hospitals electronic record system. Demographics, American Society of Anesthesiologists physical status (ASA-PS) [8], smoking status (active smoking or not currently smoking), perioperative and postoperative data was collected. Information surrounding the anaesthetic technique, including the total dose of bupivacaine; dose of intrathecal morphine; uterotonic agents and antiemetic medications were extracted.

The primary outcome of this study was to determine the rates of PONV during the first 24 hours following the surgery when different combinations of antiemetics were given in the intraoperative period. PONV was assessed in the patient's medication chart. Patients who received rescue antiemetics in the postoperative period were considered to have had one episode of PONV. Secondary outcome focused on the efficacy of dexamethasone when added to one, two or three other classes of antiemetics. We also analysed the impact of modifying factors, such as ITM dose, naloxone use, different uterotonics agents and postoperative opioid use in the rates of PONV.

Uterotonic agents to prevent post-partum haemorrhage (PPH) used at FSH were carbetocin or oxytocin. As per institution protocol, carbetocin 100 micrograms is administered as a bolus after the delivery of the baby and oxytocin is administered as a bolus (3–5 units) followed by an infusion of 10 units per hour over 4 hours.

The choice of drugs given in intrathecal space, namely bupivacaine and intrathecal morphine dosage and the postoperative analgesic regimen was at the discretion of the specialist anaesthetist and the obstetric team supervising the care of the patient. Antiemetics commonly used for prophylaxis of PONV included: serotonin ($5HT_3$) receptor antagonists (e.g., ondansetron), dopaminergic antagonists (e.g., droperidol. metoclopramide), histamine antagonists (e.g., cyclizine) and corticosteroids (e.g., dexamethasone). The selection of the antiemetic prophylaxis was at the discretion of the individual anaesthetist caring for the patient. The most frequently prescribed opioid based analgesics were oral tramadol and sublingual buprenorphine.

Statistical analysis

Analyses were completed including comparisons between antiemetic combinations with and without dexamethasone, the impact of ITM dosage and uterotonic use and other factors known to modulate the rate of PONV.

Data was collated in a password protected Microsoft Excel spreadsheet and analysed in SPSS Version 26 (IBM Corporation, Armonk, New York, United States). Data is presented as number and percentage or median and interquartile range for categorical and continuous variables respectively following normality testing. The Chi Square test (with or without an appropriate continuity correction) or the Fisher Exact test were used for categorical data while the Mann-Whitney U-test was used for continuous parameters. A multivariate model using backwards elimination was constructed following univariate comparisons to determine the predictors of PONV following caesarean delivery. A two-tailed *p*-value of less than 0.05 was used to define statistical significance.

Table 1. Baseline demographics.

	No PONV	PONV	*p*-value
Number (percent)	424 (71.0)	174 (29.0)	-
Age (years)	33 (29–36)	34 (29–36)	0.41
Weight (kilograms)	80 (69–94)	82 (72–95)	0.17
Body Mass Index (kg/m^2)	29.7 (26.3–34.0)	31.2 (27.0–35.8)	0.05
Gravida	2 (2–3)	3 (2–3)	0.17
Parity	1 (1–2)	1 (1–2)	0.08
Cigarette smoker	39 (9.2)	7 (4.0)	0.03
ASA-Physical Status Score			0.63
- 2	409 (96.7)	167 (96.0)	
- 3	14 (3.3)	7 (4.0)	
Surgical Duration (minutes)	60 (60–90)	60 (60–90)	0.76
Bupivacaine Dose (milligrams)	11.5 (11.0–12.0)	11.5 (11.0–12.0)	0.19
Intrathecal morphine (micrograms)	100 (100–150)	150 (100–150)	<0.001
Uterotonic use			
- Oxytocin	289 (68.5)	133 (76.4)	0.06
- Carbetocin	133 (31.5)	41 (23.6)	0.06
- Ergometrine	2 (0.5)	3 (1.7)	0.15
- Carboprost	0 (0.0)	1 (0.6)	0.29
Naloxone	53 (12.5)	0 (0.0)	<0.001
Post-procedure oxycodone with naloxone use	13 (3.1)	28 (16.1)	<0.001
Number of Antiemetic Drugs	2 (1–3)	2 (1–2)	<0.001
- 0	42 (9.9)	25 (14.4)	
- 1	102 (24.1)	61 (35.1)	
- 2	161 (38.0)	64 (36.8)	
- 3	106 (25.0)	20 (11.5)	
- 4	13 (3.1)	4 (2.3)	

Data is presented as number (percent) or median (interquartile range) as appropriate.

Two tailed *p*-values of <0.05 defines statistical significance.

No correction has been applied for multiple testing.

PONV, Postoperative Nausea and Vomiting; ASA, American Society of Anesthesiologists.

3. Results

Between the 1st January 2016 and the 31st October 2017, 686 women underwent elective caesarean delivery. After the exclusion of 88 patients, 598 (87.2%) patients remained (Fig. 1). PONV occurred in 174 (29%) parturients. There were no differences in the baseline demographics between the groups who did and did not have PONV (Table 1).

There was a significant association between the number of antiemetics used and the probability of experiencing PONV (Odds Ratio = 0.70 (95% CI: 0.58–0.84), $p < 0.001$, $R^2 = 0.04$), indicating that PONV decreases with moderate effect as the number of antiemetics administered increases. Subgroup analysis showed that patients receiving 0, 1, 2, 3 or 4 antiemetic medications had rates of 37%, 37%, 28%, 16% and 23% of PONV (Table 2). There was no statistically significant difference in the incidence of PONV between patients who received zero and one antiemetic ($p = 0.56$) and one and four antiemetics ($p = 0.194$) (Table 2). The number of antiemetics administered accounts for 31.8% of the variability in PONV ($R^2 = -0.318$). There was a statistically significant difference in the incidence of PONV between patients who received one and two antiemetics ($p = 0.062$); one and three antiemetics ($p = 0.001$) and two and three antiemetics ($p = 0.008$). The median number of antiemetics across the entire cohort was 2 (interquartile range 1–2). Those in PONV group received less antiemetic prophylaxis than those in non-PONV group (2 (1–2) versus 2 (1–3), $p < 0.001$).

Larger doses of ITM were associated with higher rates of PONV ($p < 0.001$) (Table 3). There were significant differences in the PONV rate between those who received 100 mcg versus 150 mcg of intrathecal morphine ($p < 0.001$) and those who received 125 mcg versus 150 mcg ($p = 0.02$). However, no significant difference was found with doses of a 100 mcg and 125 mcg ($p = 0.52$).

There was no difference in the use of both carboprost ($p = 0.15$) and ergometrine ($p = 0.15$) between the two

Table 2. Number of or combinations of antiemetics and PONV rates.

	No PONV	PONV	*p*-value
Metoclopramide use	180 (74.4)	62 (25.6)	
Ondansetron use	335 (73.6)	120 (26.4)	
Dexamethasone use	180 (75.0)	60 (25.0)	Testing not completed
Droperidol use	56 (80.0)	14 (20.0)	
Cyclizine use	42 (84.0)	8 (16.0)	
No drugs	42 (62.7)	25 (37.3)	
One drug	102 (62.6)	61 (37.4)	
Two drugs	161 (71.6)	64 (28.4)	0.001
Three drugs	106 (84.1)	20 (15.9)	
Four drugs	13 (76.5)	4 (23.5)	
Dexamethasone alone	4 (80.0)	1 (20.0)	
Dexamethasone plus one drug	86 (69.4)	38 (30.6)	0.14
Dexamethasone plus two drugs	81 (82.7)	17 (17.3)	
Dexamethasone plus three drugs	9 (69.2)	4 (30.8)	
	PONV Rate Group One	PONV Rate Group Two	*p*-value
Zero versus one drug	25 (37.3)	61 (37.4)	1.00
Zero versus two drugs	25 (37.3)	61 (28.4)	0.18
Zero versus three drugs	25 (37.3)	20 (15.9)	0.001
Zero versus four drugs	25 (37.3)	4 (23.5)	0.40
One versus two drugs	61 (37.4)	64 (28.4)	0.08
One versus three drugs	61 (37.4)	20 (15.9)	<0.001
One versus four drugs	61 (37.4)	4 (23.5)	0.30
Two versus three drugs	64 (28.4)	20 (15.9)	0.009
Two versus four drugs	64 (28.4)	4 (23.5)	0.79
Three versus four drugs	20 (15.9)	4 (23.5)	0.49
Dexamethasone alone versus one drug without dexamethasone	1 (20.0)	59 (37.6)	0.65
Dexamethasone plus one drug versus two drugs without dexamethasone	38 (30.6)	26 (25.7)	0.46
Dexamethasone plus two drugs versus three drugs without dexamethasone	17 (17.3)	3 (10.7)	0.56
Dexamethasone plus three drugs versus four drugs without dexamethasone	4 (30.8)	0 (0.0)	0.52

Data is presented as number (percent) or median (interquartile range) as appropriate.

Two tailed *p*-values of <0.05 defines statistical significance.

No correction has been applied for multiple testing.

groups. PONV was more frequent in patients who receive opioids for breakthrough pain in the postoperative period (16.1% versus 3.1%, $p < 0.001$). Both smoking ($p = 0.03$) and the use of naloxone to prevent itch ($p < 0.001$) appeared to be protective against PONV. Although the incidence of PONV was slightly higher in those who received carbetocin (31.5%) when compared with oxytocin (23.5%), no statistical difference was detected between the two drugs ($p = 0.06$). There were 576 (96.5%) of patients who were ASA-PS2 and the remaining (22) were ASA-PS3 (Table 1). There was no statistical relationship in ASA- PS scores for PONV ($p = 0.63$).

Sensitivity analyses were completed to account for factors which were known to increase or decrease the rates of PONV in patients undergoing CD [3]. Factors considered to increase the rates of PONV excluded in this analysis were Carboprost ($PGF_{2\alpha}$), ergometrine and postoperative opioids for breakthrough pain. Factors considered to

Table 3. Intrathecal morphine dose and PONV rate.

	No PONV	PONV	*p*-value
Dose of intrathecal morphine	100 (100–150)	150 (100–150)	<0.001
100 mcg	220 (77.2)	65 (22.8)	
125 mcg	29 (82.9)	6 (17.1)	<0.001
150 mcg	175 (62.9)	103 (37.1)	
	PONV Rate First Group	PONV Rate Second Group	*p*-value
100 versus 125 mcg	65 (22.8)	6 (17.1)	0.52
100 versus 150 mcg	65 (22.8)	103 (37.1)	<0.001
125 versus 150 mcg	6 (17.1)	103 (37.1)	0.02

Data is presented as number (percent) or median (interquartile range) as appropriate.

Two tailed *p*-values of <0.05 defines statistical significance.

No correction has been applied for multiple testing.

decrease the rates of PONV excluded in this analysis were Naloxone used in the postoperative period and active smokers. After removing all the potential biases from the main analysis, a significant statistical difference remained between the number of antiemetics given in the intraoperative period and the occurrence of PONV ($p < 0.001$).

To determine the effect of different combinations of antiemetics exploratory analyses were completed. Some of these tests were limited by statistical power and we could not analyse drugs in combination apart from dexamethasone. Overall, 240 (40.1%) patients received dexamethasone. Only 3.1% (5/163) of the patients received this medication as a solo antiemetic. Patients who received two, three or four antiemetics, had dexamethasone as part of the combination in 55.1% (124/225), 77.8% (98/126) and 76.5% (13/17) of the times respectively. There was no difference in the PONV rate between patients who did and did not receive dexamethasone (25.0% versus 31.8%, $p = 0.08$). In the subgroup analyses no difference was found in the PONV rate between two or three drug combinations when dexamethasone was used or avoided ($p = 0.46$ and $p = 0.56$ respectively).

A multivariate model was constructed using backwards elimination to determine the factors associated with PONV in our patient population. Those associated with PONV were number of antiemetics used (Odds Ratio (OR): 0.69 (95% 0.57–0.84), $p < 0.001$); intrathecal morphine dose (OR: 1.01 (1.01–1.02), $p < 0.001$) and perioperative opioid use (OR: 5.5 (2.7–11.2), $p < 0.001$). The R^2 value was 0.22.

4. Discussion

This study showed that nausea and vomiting are still common complications in the postoperative period in parturients undergoing caesarean delivery with intrathecal morphine. We found that exposure to a greater number of antiemetics was protective. However, we did not find any benefits of dexamethasone either on its own, or when combined to one, two or three other antiemetics.

In our study, approximately 37% of women who did not receive antiemetic prophylaxis experienced PONV. In comparison, two studies found PONV rates of 67% and 35% when placebo was used in one of the arms [2,9]. Differences between the doses of ITM given and the management of uterotonic agents in the perioperative period may explain part of these discrepant findings. These same studies demonstrated that the PONV rate decreased by more than 50% when one antiemetic was used. In contrast, patients who received only one antiemetic in our study continued to experience similar rates of PONV as the group who did not have antiemetic prophylaxis. However, these rates significantly decreased to 28%, 16% and 23% in women who received two, three or four antiemetics respectively. To our knowledge, this is the first study to analyse the rates of PONV in patients receiving such a diverse combination of antiemetics in the intraoperative period. The lack of studies comparing various combinations of antiemetics other than dexamethasone is part explained by the difficulties associated with conducting research using multiple arm groups and the element that some of the antiemetics may pose a low theoretical risk to the neonate [10,11]. As a result, there is a lack of consensus to the best regimen to prevent this complication and combinations selected by anaesthetists are often ad hoc and many avoid using some of the agents.

A few studies assessed the rate of PONV when one or two drugs are used in the context of intrathecal morphine. When compared with placebo, serotonin antagonists, dopaminergic antagonists such as droperidol and histamine H1 antagonists have all shown to be effective as single agents while the evidence for dexamethasone is lacking [2–6]. Studies comparing dexamethasone as a single agent to placebo could not demonstrate benefits of this medication for PONV prophylaxis [2,4,5]. Moreover, when used in combination with another antiemetic, only one study was able to find a marginal benefit of this medication when combined with droperidol [6]. Our study didn't show any benefit of dexamethasone when combined with either one, two

or three other antiemetics. This further reinforces the current literature which suggests there is no evidence supporting the use of dexamethasone for PONV after CD [2–5].

We also found that larger doses of intrathecal morphine and the use of postoperative opioids for breakthrough pain led to greater rates of PONV. It is known that increasing the dose of ITM will increase the risk of side-effects such as PONV, pruritus and urinary retention [12]. Moreover, ergometrine and carboprost used as second line agents to promote uterine contraction can also precipitate nausea and vomiting through their diffuse mechanisms of action including agonism at serotonin and dopamine receptors and augmentation of oxytocin release respectively [1]. These factors were considered potential biases that could have increased the rates of PONV in our study. On the other hand, factors that could have potentially decreased the rates of this complication were antiemetics given in the intraoperative period, the use of the opioid receptor antagonists naloxone in the postoperative period and active smoking patients, which is a known protective factor for PONV [13]. After correcting for these cofounders, a statistically significant difference in the number of antiemetics administered and the rates of PONV remained.

In our population both carbetocin and oxytocin were used as uterotonic agents following the delivery of the foetus to promote uterine contraction and prevent PPH. Both these drugs are a known risk factor for intraoperative emesis [1]. Despite this association, little is known about the impact of these drugs on PONV. Their use is mandatory in those undergoing caesarean deliveries and therefore, comparisons to those who did not receive the drug was not possible. In this study we found no differences in the rate of post-operative nausea and vomiting between carbetocin and oxytocin. These results may however be institution specific due to the variability in oxytocin bolus and infusion regimens which exist between centres [14].

In this study, dexamethasone was the most frequent medication used in combination with multiple other classes of antiemetic. For this reason, this research lacks the statistical power and sample size to draw stronger conclusions including suggestions as to which combinations of antiemetic drugs are the most efficacious in this setting. Although the use of three or even four agents may reduce the rate of PONV further, these results may be confounded by patients who experienced intraoperative nausea and vomiting or patients who had significant risk factors for PONV which may make the data more complex to interpret. It is difficult to ascertain the reason why multiple drugs were used as the medical record in place often lacked comments explaining why various drug combinations were used. Independently, patients who received more antiemetics had lower rates of nausea and vomiting in the postoperative period.

The external validity of this study may be limited by some factors. We did not collect data on patient comorbidities such as gestational diabetes or hypertension to determine their effect on PONV rates. As a surrogate we used the ASA-PS score. Most patients in this cohort were ASA-PS 2 which may indicate a discrepancy on how clinicians judge which patients are ASA-PS 2 or ASA-PS 3 or the patients which were included had a normal pregnancy or had controlled gestational hypertension, diabetes or preeclampsia [8]. Therefore, patients who have a complicated gestation (ASA-PS 3) may require different antiemetic therapy. Moreover, with the worldwide trend towards an increase age at the time of first pregnancy, our results may not be extrapolated outside of this population since most of the cohort were in their fourth decade of life. Finally, this study examined the rate of PONV in a group of patients undergoing elective CD where ITM was used for post-operative analgesia. These results may not be valid in those undergoing emergent CD or where alternative additives are used in the intrathecal injectate.

5. Conclusions

We have shown that the rate of postoperative nausea and vomiting after elective caesarean deliveries when intrathecal morphine is used was inversely related to the number of antiemetics given in the intraoperative period. Moreover, dexamethasone did not show to provide any benefit to prevent PONV when added to one, two or three antiemetics. Future research is warranted to determine the optimal combination of drugs to reduce PONV without maternal and neonatal complications associated with their use.

Author contributions

MEK First author—Study design, data collection and manuscript writing. NJL—Study design, Statistical analysis, data analysis and manuscript writing. YO—Study design, data collection and manuscript writing. JYC—Data collection and manuscript writing. HSM—Study design and data collection. DWH—Study design and data collection. EJO, principal investigator—Study design, data collection and manuscript writing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This project received approval as a quality assurance project through the Quality Improvement office at the Fiona Stanley Hospital via the GEKO (Governance, Evidence, Knowledge, Outcomes) system—reference number 23664. Informed consent was not obtained as this was a retrospective cohort study.

Acknowledgment

The authors would like to recognise all the support offered for this research from the Mackay Institute of Research and Innovation (MIRI). Special thanks for Dr. David Farlow. Also, the authors would like to express gratitude

for the Fiona Stanley Hospital Department of Anaesthesia, especially Dr Edmond J O'Loughlin and his vision for research that made this project possible.

Funding

Funding to conduct this study was provided by the Mackay Hospital and Health Service. Grant: Mackay Institute of Research and Innovation (MIRI) granted 5000 Australian dollars for research. Reference: MIRI2020-04.

Conflict of interest

The authors declare no conflict of interest.

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