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Title Page

Pre-operative intratympanic gentamicin in patients undergoing retrosigmoid resection of large vestibular schwannomas: a pilot study

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Pre-operative intratympanic gentamicin in patients undergoing retrosigmoid resection of large vestibular schwannomas: a pilot study

Abstract

Purpose: To assess the impact of intratympanic (IT) gentamicin on the recovery of patients with large vestibular schwannomas (VS) undergoing retrosigmoid resection.

Methods: We conducted a prospective case-control pilot study over 24-months, including 13 patients with large VSs (25-41mm intracranial diameter); seven patients received IT gentamicin pre-operatively, while six did not. Our outcome measures were duration of stay (main), age, gender VS size, body mass index (BMI) and financial costs.

Results: Age had the highest correlation for longer inpatient stay. The non-gentamicin patients had longer hospital stay, were older, had a lower BMI and larger VS. We observed a trend towards shorter stay in patients receiving gentamicin with tumours <35mm, but not in those with larger ones; costs were lower for the gentamicin group.

Conclusion: While we did not identify statistical significance, for patients with VS >35mm there was a positive trend; thus, IT gentamicin as prehabilitation could be considered.

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Keywords

Gentamicin; Inpatient; Recovery; Rehabilitation; Resection; Vestibular schwannoma

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Introduction

Vestibular schwannomas (VS) are benign tumours that develop from the vestibulocochlear nerve sheath. (1) They generally present as unilateral, sporadic tumours that cause symptoms such as progressive hearing loss or sudden deafness, and unilateral tinnitus among other symptoms; bilateral VSs are a hallmark for Neurofibromatosis type 2, where the management is multidisciplinary and individualised due to the variety in tumour load and symptoms. (1,2) The tumour size is an important factor in decision making; the Koos classification is the most widely used ranging from grade I to IV, where grade I is an intra-canalicular tumour (<15mm), grade II is a cerebellopontine angle tumour with some extension (<20mm), grade III is similar to grade II but with greater extension and no cerebellar trunk displacement (<30mm), and lastly, grade IV is a larger tumour involving brainstem displacement (>30mm). (3)

VS management is based on several factors such as the Koos grade, tumour growth, patients' symptoms and preferences as well as age. While the indication for active treatment can vary the main management regimes include watchful waiting, microsurgical resection, or radiosurgery. Typically, for larger tumours, microsurgery is the preferred choice of treatment and is carried out most commonly via the translabyrinthine or retrosigmoid approach. (4) Acute vestibular symptoms after the surgical resection of vestibular schwannomas, such as nausea, vertigo and postural imbalance, are a key factor in the post operative recovery of the patient. (5)

Intratympanic (IT) gentamicin can be used pre-operatively to ablate remaining vestibular function. IT gentamicin is vestibulotoxic that can be used to gradually ablate peripheral vestibular function preoperatively. This prevents sudden loss of peripheral vestibular function post-operatively, which occurs due to the dissection of the vestibular nerve during tumour resection or even labyrinthectomy during translabyrinthine approach, subsequently improving vestibular compensation and post-operative recovery. (5, 6) Previous studies have shown that the use of IT gentamicin preoperatively has reduced in-patient stay in patients with small to medium sized vestibular schwannomas up to 20mm who have undergone a resection via the translabyrinthine approach. (6-9)

However, there have been very few studies that have assessed the impact of pre-operative IT gentamicin on post-operative recovery for patients after retrosigmoid resection with particular focus on larger

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tumours. Thus, our aim was to assess the impact of IT gentamicin on the duration of in-patient stay in patients with a large VS undergoing resection via the retrosigmoid approach.

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Methods

Basic settings

We conducted a prospective case control pilot study over a 24-month period in a tertiary university centre. Ethical approval was granted by the local Ethical Committee; additional informed consent was obtained by each patient.

Patient selection

We included patients who underwent a retrosigmoid resection of a large VS; we enrolled a total of 13 patients, where seven received IT gentamicin pre-operatively while six did not. We included patients with large sporadic VS only, which were classified as Koos grade III and IV. The use of IT gentamicin was discussed with all patients, who subsequently decided to opt in or out. The main reasons not to pursue pre-operative injections were the patient's preference not to have any intervention prior to the VS resection and the need for semi-urgent surgery, which did not allow time for IT injections.

In addition, we only included patients with no serviceable hearing and who had no previous intervention for their VS.

IT injections

In patients who received IT gentamicin preoperatively, two to three injections of 40mg/ml solution of gentamicin (0.6-0.8ml solution) were administered into the middle ear with a 22-gauge spinal needle under topical anaesthesia. An interval of one week between injections allowed patients to be assessed clinically and via video head impulse test to determine whether additional injections were needed.

The intratympanic gentamicin administration and subsequent retrosigmoid resections of the VS took place in the same tertiary university centre.

Outcome measures

Our main outcome measure was duration of inpatient stay while additional analysed factors were: age, gender, vestibular schwannoma size, and body mass index (BMI in kg/m^2) as well as financial cost of

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in-patient stay based on surgical bed occupation (surgical costs related to resection not included, as these are standardised).

VS size was determined by Magnetic resonance imaging (MRI) scans conducted pre-operatively, recording in mm the maximum intracranial component only, and classified according to Koos classification, where all the patients have a grade III VS and above. (3)

In-patient stay was counted in days from the day of operation to the day of discharge.

Cost analysis was based on the emergency surgical bed from the Scottish population. (10) Only costs related to in-patient admission and not to the actual theatre time were calculated in British pound sterling.

Smoking was taken into consideration but none of the patients were smokers, hence, this was excluded.

In addition, co-morbidities were heterogeneous and as a result; this was also excluded.

Analysis

We used Jamovi (version 2.3) with R language and associated packages. (10-14) Shapiro-wilk test was used to assess the data distribution. Unpaired t-test (t) was utilized in parametric data while the Mann Whitney U-test (u) for non-parametric data. Subsequently, in-patient duration correlations against the explored co-variates of interest were explored with Pearson (r) or Spearman (rho) correlation based on data distribution. Linear regression analysis was also performed to evaluate the impact of the covariates on in-patient stay. Statistically significant value was set at 0.05.

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Results

Basic Demography

Overall, 13 patients (Table 1) were evaluated; six patients received IT gentamicin injections pre-operatively while seven patients underwent VS resection without. VS size ranged from 25mm to 41mm (Grade III to IV), and all patients underwent retrosigmoid VS resection. Those that did not received IT gentamicin injection pre-operatively had a slightly longer hospital stay, were older, had a lower BMI and a larger VS size (Table 1). Nevertheless, no statistically significant differences were seen between the cohort for age (year-old), BMI (kg/m^2), VS size (mm) and in-patient duration (days) (Table 1).

Correlation for In-patient stay

Overall, age has the highest correlation for longer duration of in-patient stay (r: 0.52, p:0.069, Table 2) but not statistically significant. This impact was more significant, however, in those who received gentamicin pre-operatively (r:0.77, p:0.044, Table 2, Fig. 1). BMI has the lowest correlation with in-patient duration stay and was not significant (Fig. 2).

Interestingly, there is a correlation for those with larger VS size who received gentamicin to require longer in-patient stay, though not significant (r: 0.61, p:0.142, Table 2, Fig. 3). As Fig. 3 demonstrates, while patients with large VSs but smaller than 35mm who receive IT gentamicin tend to spend less days in hospital, patients from the same group but larger tumours tend to stay longer.

Linear Regression Modelling Base on Intratympanic Gentamicin Exposure

In-patient hospital duration for those that did not receive intratympanic gentamicin injection is weakly affected by age, BMI and VS size in 45% (R^2) of patients here and is not statistically significant (F: 1.63, p: 0.257, Adjusted R^2: 0.174, AIC: 70.5, Table 3). This was also seen based on the minimum and maximum cost that it could incur.

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Discussion

Main findings

Several studies have demonstrated a statistically significant impact on post-operative recovery and use of pre-operative IT gentamicin injections in patients undergoing mostly translabyrinthine resection of a small to medium sized VS, up to 20mm, and very few studies for larger VS greater than 25mm. (5-9, 16) Herein, we assessed the impact of prehabilitation with IT gentamicin on patients with large VSs only undergoing resection, exclusively via the retrosigmoid approach. While our results did not reach statistical significance, we observed a tendency for shorter in-patient duration in the IT gentamicin group in patients with tumours smaller than 35mm intracranial diameter; patients from the same group with larger VSs stayed longer in the hospital. Additionally, younger age was statistically linked to shorter in-patient stay regardless the use of gentamicin; BMI had no effect on the duration of stay.

While our results are preliminary, it is sensible to consider the use of IT gentamicin as prehabilitation in patients with VSs smaller than 35mm undergoing retrosigmoid approach but not in patients with larger tumours. Further research in this evolving field should be encouraged.

The concept of prehabilitation with IT gentamicin

IT gentamicin is a vestibulotoxic substance that can ablate peripheral vestibular function; previous studies have highlighted its benefits when used as prehabilitation in patients undergoing VS resection in the sense that gentamicin allows a more 'gentle' ablation of the vestibular function prior to the instant and radical impact of the VS and vestibular nerve resection as well as labyrinthectomy (in translabyrinthine approach). (5-9, 16) In particular those studies focused primarily on postoperative postural control, quality of life and vestibular testing as outcome measures (5-9), while only one study assessed the duration of the in-patient stay (16). Most of these studies included a wide range of tumour sizes and predominantly translabyrinthine resections. Our study assessed exclusively large tumours resected through the retrosigmoid approach; these inclusion criteria can explain, to some extend the results.

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Indeed, it is sensible to hypothesize that the combined impact of tumour dissection, vestibular nerve resection and labyrinthectomy in translabyrinthine approaches, is more severe than the one in retrosigmoid approaches where the labyrinth is anatomically preserved. The first report of the concept of prehabilitation with IT gentamicin did not emphasize on the approach; however, it did demonstrate absence of true vertigo postoperatively, which enhanced the patients' recovery (18) Reports purely looking into retrosigmoid VS resections did not show statistically significantly better vestibular compensation for the gentamicin groups in the early postoperative period (5, 19); however, they did show significantly lower levels of patient anxiety and less sensitivity to optokinetic stimulation (19), factors that can both improve the recovery. Still, both of the above studies included a wider range of VS size compared to our study. The only study including only patients with large VSs (Koos III and beyond) by Amiraraghi et al (16) only included patients undergoing translabyrinthine resections, concluding on significantly shorter duration of stay and milder impact on the contralateral side as assessed through six-canal video head-impulse test.

While one could argue any contralateral impact of IT gentamicin, a negative effect has not been proven in human. Indeed, animal studies have identified traces of gentamicin following IT administration, in the contralateral inner ear of chinchilla (only light anti-gentamicin staining was observed), probably migrating to the contralateral ear through a pathway involving the cochlear aqueducts, without clarifying what the exact clinical implication of such laboratory finding could be (20). However, such result has not been evident in human. On the contrary, previous study has shown that in patients with VS undergoing translabyrinthine resection, who have had IT gentamicin, they all had normal contralateral vestibular responses six-weeks postoperatively, while the ones who did not, had abnormal responses from at least one contralateral semi-circular canal (16). This would indicate, that by ablating the vestibular responses in a more gradual manner, preoperatively, the contralateral ear had to work less hard to compensate (16). On these grounds, one would identify a potentially positive effect of gentamicin on the contralateral ear, at least in this specific group of patients.

Our current results showed some tendency for shorter stay for the gentamicin group with tumours smaller than 35mm but still absence of any statistical significance. This can be either because of the small numbers or due to an overall 'milder' direct impact on the vestibular organ through the

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retrosigmoid approach; both explanations remain a hypothesis. For even larger tumours, IT gentamicin did not carry any benefits; on the contrary, patients seemed to stay longer. A probable hypothesis for such observation would be the direct impact of such large tumours as well as the subsequent surgical dissection on the brainstem and the postoperative central compensation, which is expected to be more challenging in such large tumours (>35mm intracranial diameter).

It is worth mentioning that recent systematic review identified statistically significant improvement in half of the patients treated with IT gentamicin injections prior to VS resection, highlighting the overall limited number of patients and the need for further research (9).

Financial cost and other considerations

Considering the challenges faced by the healthcare services, any potential cost-saving actions could be of benefit. While the impact of age, VS size and BMI on in-patient stay was not statistically significant, there is a benefit cost-wise as a reduced in-patient duration by 1.6 days would save £1300 to £2570, which would equate to a two-bed capacity. (10) These numbers do not include the costs of the IT gentamicin injection, which is an office/ outpatient procedure and therefore carries minimal costs. Even in the absence of statistical significance in in-patient duration, the admission costs were lower for every patient in the gentamicin group compared to the non-gentamicin one.

Another consideration point is the concept of hearing preservation in VS surgery. Should such concept be explored, then the injection of gentamicin should be arguable given the potential impact of such medication on hearing. In our study, none of the patients had serviceable hearing pre-operatively, hence the concept of hearing preservation was not relevant. Furthermore, in patients with such large tumours, even via the retrosigmoid approach, hearing loss should be expected even if any degree of hearing is measurable prior to the procedure. (17)

While our results did not reach statistical significance, we observed a tendency for shorter in-patient duration in the IT gentamicin group but only for patients with tumours smaller than 35mm intracranial diameter; patients from the same group with larger VSs stayed longer in the hospital. Additionally, younger age was statistically linked to shorter in-patient stay regardless the use of gentamicin; BMI had no effect on the duration of stay.

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Limitations and strengths

The main limitations of this study are primarily related to the small size of the cohort, where a possible selection bias due to a small sample size could limit the randomization process and increase the potential of error. However, this was mitigated by conducting a thorough data collection using standardized detailed measurements, and subsequent meticulous statistical analysis via a generalized linear model as well as appropriate statistical tools. While we used duration of inpatient stay as our main outcome measure, we accept that additional/ alternative measures, probably less quantifiable, can be used to assess patient recovery. Additionally, this is a pilot study and further evolving reports are pending.

On the other hand, there are several strengths to this study, the main one being the prospective nature of the data collection. Longitudinal analysis provides greater insight into outcomes that may be different among groups, thus limiting selection bias and strengthening the study in comparison to other similar studies with retrospective data collection. In addition, the novelty of this study is a strong point as most of the existing studies in this field have assessed either smaller tumours or a mixture of sizes and approaches; we focused on only retrosigmoid approach and large tumours that typically involve more time-demanding and challenging dissection and postoperative care.

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Conclusion

This pilot study did not show any statistically significant impact of IT gentamicin on in-patient hospital stay in patients with large VSs undergoing retrosigmoid resections. We did observe a trend towards shorter stay in patients receiving gentamicin with tumours smaller than 35mm but for larger tumours the IT injections were not beneficial. Despite the absence of statistical significance, costs related to in-patient stay were less for the gentamicin group. Finally, younger patients had shorter in-patient stay.

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Declarations

Conflict of interest and financial disclosure

None to declare

Ethical Standards

Ethical approval and informed consent obtained

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Author Contribution

TP: data curation and analysis, writing and revising the initial and final draft, approval of the final draft; **MAMS:** data analysis, writing and revising the initial draft, approval of the final draft; **GK:** conceptualisation, data analysis, revising the initial draft, finalising and approving the final draft, supervision

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Bullet Point Summary

- Preoperative IT gentamicin injections have shown the potential of improved recovery following vestibular schwannoma (VS) resection.
- In our pilot study, focusing on purely patients with large tumours operated via the retrosigmoid approach, we did not find statistically significant impact of the IT gentamicin injections on the duration of inpatient stay.
- However, we did observe a trend towards shorter stay in patients with large VS but smaller than 35mm in the cerebello-pontine angle but not for patients with even larger tumours.
- Overall, younger patients demonstrated shorter duration of stay.
- Despite the absence of statistical significance in the duration of inpatient stay, the associated costs of stay for the gentamicin group were significantly less; this is an important factor for the health services.

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Legends for Figures

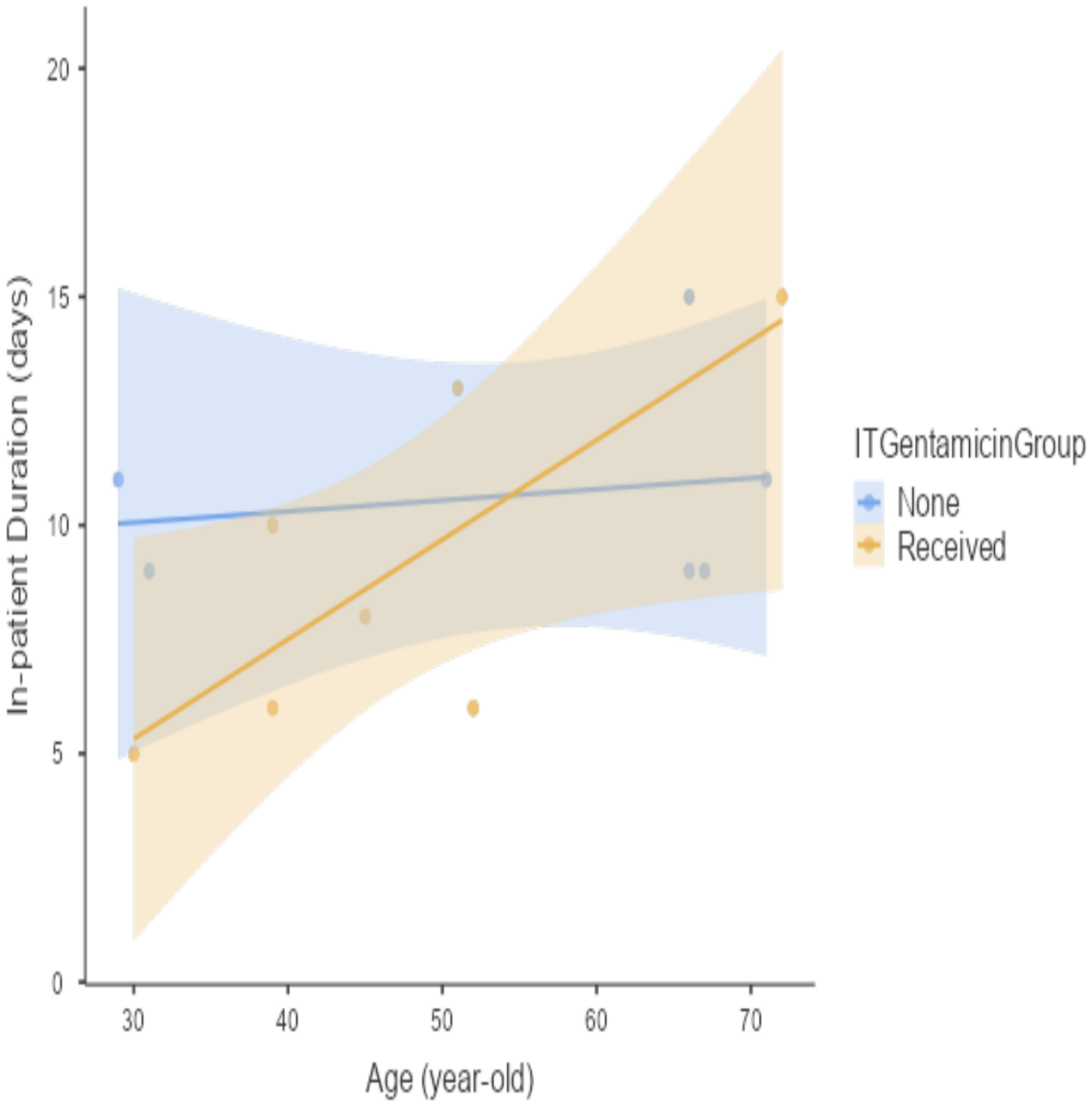

Figure 1: Scatter plot for Age vs In-patient stay

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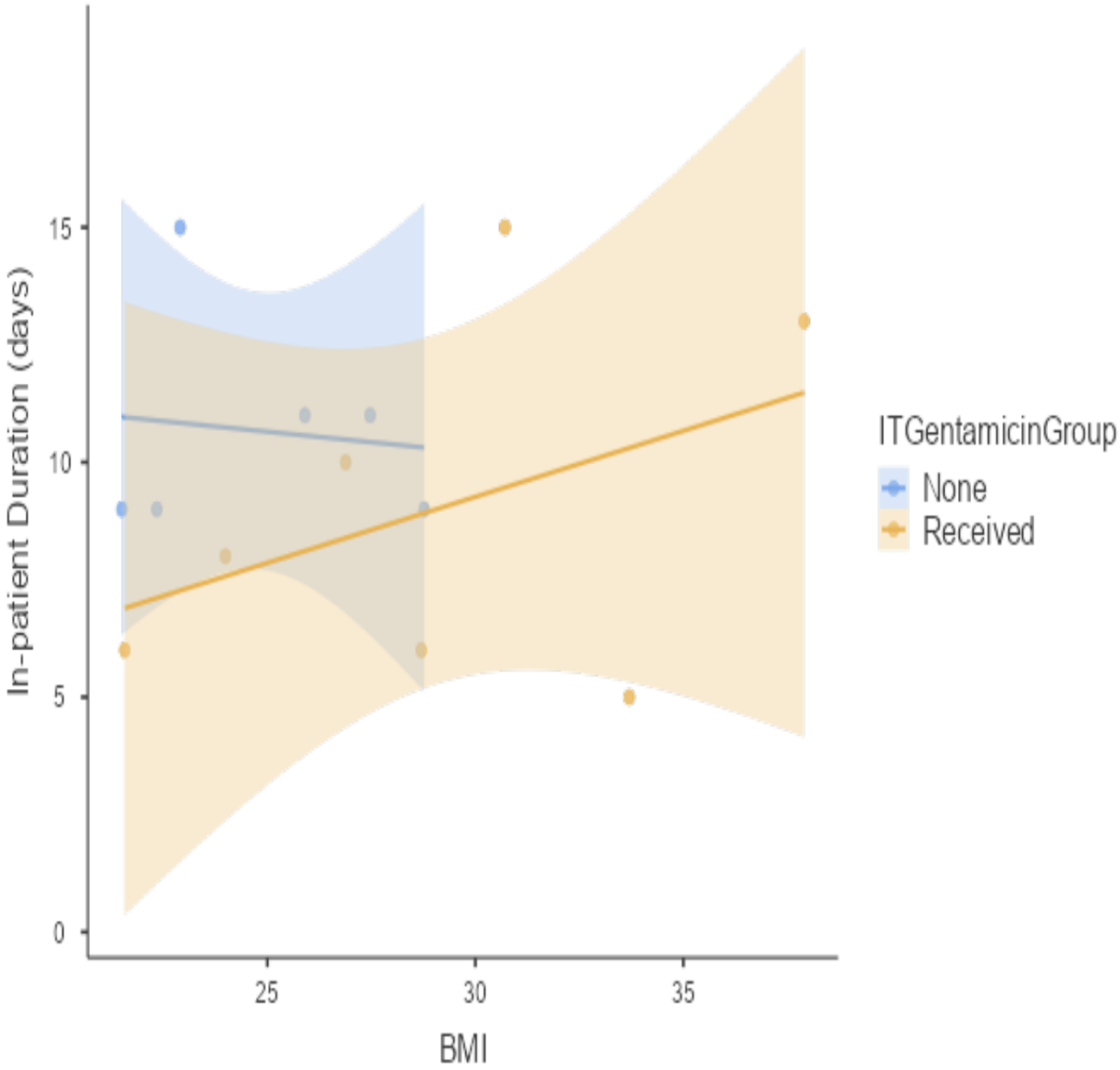

Figure 2: Scatter plot for BMI vs In-patient stay

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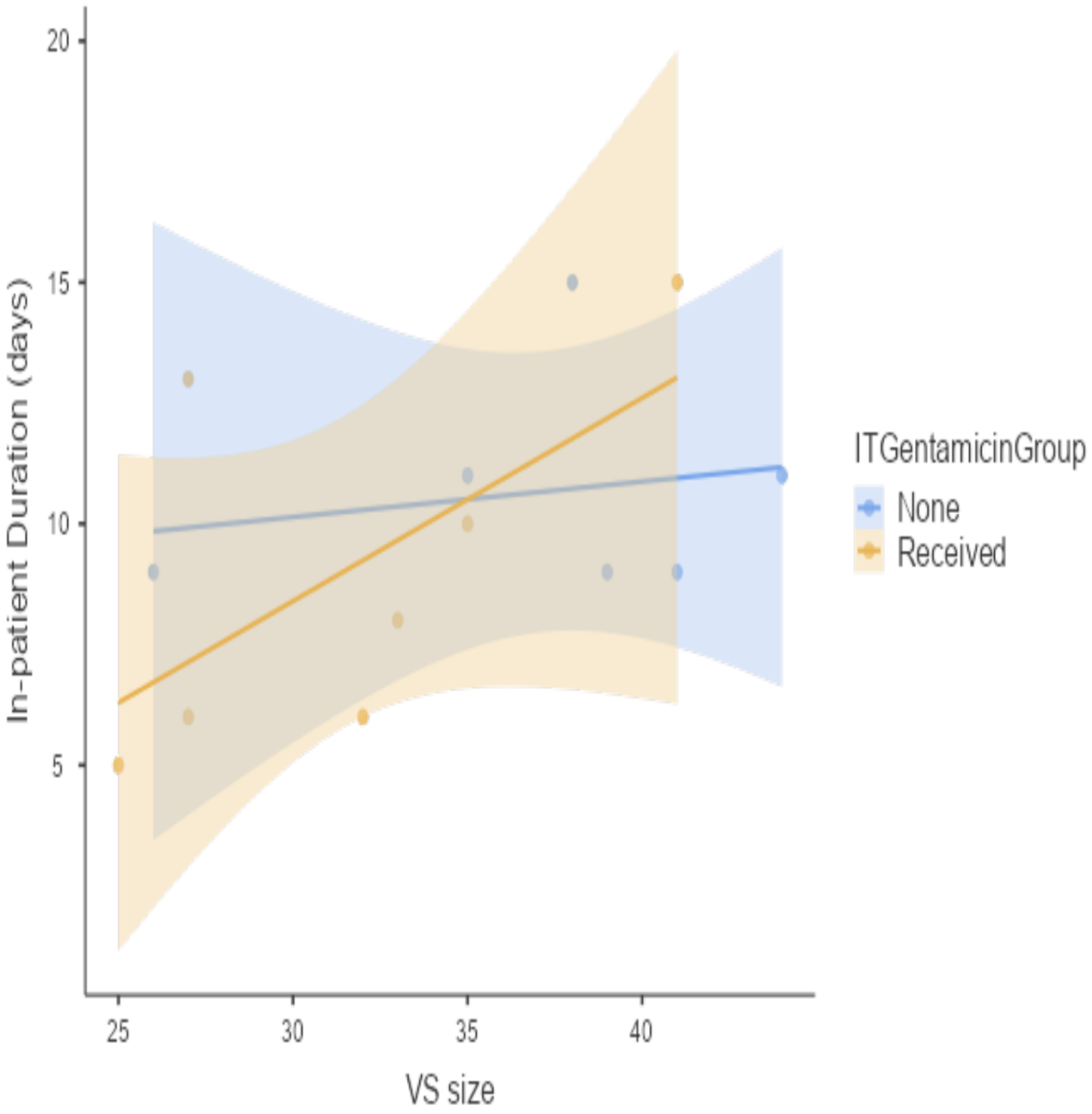

Figure 3: Scatter plot for VS size vs In-patient stay duration; interestingly, IT gentamicin is linked to shorter stay for patients with large VSs but smaller than 35mm but to longer stay for patients with larger than 35mm VS.

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Table 1. Basic demography and recorded data

	Average (SD) (n=13)	Intratympanic Gentamicin			p-value
		Not Received (n=6)	Received (n=7)	Mean Differences	
Age (year-old)	50.6 (16.3)	55.0 (19.5)	46.9 (13.5)	8.14	0.393 [t]
BMI (kg/m^2)	27.1 (4.93)	24.8 (2.99)	29.1 (5.61)	-4.25	0.126 [t]
VS Size (mm)	34.1 (6.38)	37.2 (6.24)	31.4 (5.59)	5.74	0.108 [t]
In-patient Duration (days)	9.77 (3.22)	10.7 (2.34)	9 (3.83)	1.67	0.375 [t]
Minimum Cost	7679 (2530)	8384 (1838)	6288 (3010)	1310	0.375 [t]

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Maximum Cost (£)	13806 (4937)	16363 (3587)	13806 (5875)	2557	0.375 [t]

[t] unpaired t-test

Table 2. In-Patient Duration Correlations (Pearson correlation, r)

	Overall (n=13)	p-value	Intratympanic Gentamicin			
			Not Received (n=6)	p-value	Received (n=7)	p-value
Age (year-old)	0.52 [-0.05; 0.83]	0.069	0.20 [-0.73; 0.87]	0.701	0.77 [0.03; 0.96]	**0.044**
BMI (kg/m^2)	0.14 [-0.45; 0.64]	0.654	-0.11 [-0.85; 0.77]	0.829	0.41 [-0.49; 0.89]	0.358
VS Size (mm)	0.50 [-0.07; 0.83]	0.079	0.20 [-0.73;0.87]	0.709	0.61 [-0.26;0.93]	0.142

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